

Chapter 2

Pharmacology of TRP Channels

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Abstract TRP channels are a family of ion channels involved in a plethora of physiological sensory processes. Since their discovery they have attracted the attention of academic and non-academic laboratories with the aim of developing modulators that could be used as pharmacological tools for unveiling their physiological and pathological activities, and as therapeutic compounds for intervening in TRP dysfunction. Intriguingly, TRP pharmacology shows dispersed progress, with vast pharmacology developed for some members of the so-called thermoTRP channel subfamily (TRPV1, TRPV3, TRPM8 and TRPA1), and very little, for all other TRP channels. Pharmacologically, the most investigated TRP channel is undoubtedly TRPV1 for which a large number of agonists and antagonists with *in vitro* and *in vivo* activities have been characterized. Recent interest has grown for TRPV3, TRPM8 and TRPA1 because of their implication in several human pathologies and disorders. Similarly, the TRPM3 channel is emerging as important targets for pain transduction. With the development of novel screening methods, the focus is slowly changing to other TRP members for whom we do not have appropriate agonists or antagonists. These include the TRPC family, which has limited our understanding of their role in pathological processes and whether pharmacological intervention in these channels will have a therapeutic benefit. A bright future is anticipated for TRP pharmacology, with the discovery of selective and potent modulators for this important family of sensory channels.

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© Springer International Publishing Switzerland 2015
R. Madrid, J. Bacigalupo (eds.), *TRP Channels in Sensory Transduction*,
DOI 10.1007/978-3-319-18705-1_2

Keywords TRP channels · Agonists · Antagonists · Competitive · Non-competitive · Uncompetitive · Pain · Therapeutic index · Pathology

2.1 Introduction

TRP channels are a superfamily of ion channels that includes seven subfamilies, namely TRPC, TRPV, TRPP, TRPM, TRPA, TRPML, and TRPN. These channels perform a wide diversity of physiological functions and are present in many tissues, and almost all cell types. Most TRP channels are non-selective cation channels with low voltage dependence. TRP channels use a wide variety of activation and regulatory mechanisms and carry out functions as diverse as thermosensation, phototransduction, pheromone reception, magnesium homeostasis, and vascular tone regulation (Montell 1999) (see Chap. 4 by Bacigalupo et al. in this Book). Thus, these channels are considered molecular gateways in sensory and regulatory systems.

Structurally, TRP channels are tetrameric assemblies of basic subunits organized around a central aqueous pore. Akin to voltage-gated K^+ channels, each subunit is composed of a transmembrane region containing 6 transmembrane segments. The recent structural model derived from cryo-electron microscopic images has clearly shown this molecular analogy (Liao et al. 2013). All TRP channels display this core transmembrane region, and differ in the cytosolic N- and C-termini domains, which are involved in channel gating and mediating intracellular signaling. Indeed, most of TRP channels, if not all, are part of protein complexes known as signalplexes (Devesa et al. 2011; Fernandez-Carvajal et al. 2011; Ferrer-Montiel et al. 2012).

Some TRP channels have been involved in the pathophysiology of human diseases. This pathological contribution could be the result of channel mutations, giving rise to channelopathies (Devesa et al. 2011; Fernandez-Carvajal et al. 2011; Ferrer-Montiel et al. 2012), or the change in channel function due to alteration of the protein function and/or expression (Devesa et al. 2011; Fernandez-Carvajal et al. 2011; Ferrer-Montiel et al. 2012). The pivotal involvement in the etiology of pathological conditions has signaled members of this large channel family as druggable targets for therapeutic intervention, which has driven discovery programs in academic and non-academic institutions. This concerted effort has notably expanded the pharmacology of TRP channels, although, unfortunately, for a limited number of TRP members. For instance, large families of modulators have been obtained for TRPV1, TRPV3, TRPM8 and TRPA1, while the pharmacology of other TRP channels is still in its infancy. A plausible reason for the pharmacological progress in these channels is the availability of natural ligands present in food spices. Nonetheless, the development of combinatorial chemistry and the large diversity of vegetal and marine extracts, along with the development of high throughput electrophysiological assays for ion channels will expand the pharmacology of TRP channels to the entire family. Here, we briefly expose the pharmacological data for the most studied TRP channels, namely TRPV1, TRPM8 and TRPA1, and include the data accrued for TRPV2, TRPV4, TRPM3 and the TRPC5, most of them with an

important role in sensory transduction. We aim to illustrate the differential pharmacological progress in this exciting field and evidence a drift towards enhancing the pharmacology of other members, if not all, of this pivotal channel family.

2.2 TRPV1

TRP Vanilloid 1, TRPV1, a non-selective Ca^{2+} channel is a TRP channel activated by noxious temperatures (43 °C) acidic pH and vanilloid compounds, whose channel activity is highly potentiated by proalgesic mediators in response to inflammation, tissue injury and ischemia (Huang et al. 2006; Ueda et al. 2008). In addition, TRPV1 expression is markedly up-regulated under acute inflammatory conditions (Camprubi-Robles et al. 2009; Morenilla-Palao et al. 2004; Van Buren et al. 2005), and in human chronic pain states (Broad et al. 2008; Szallasi and Blumberg 2007). Consistent with a role in pain signaling, TRPV1 is highly expressed in C-type, peptidergic nociceptors in the peripheral nervous system. Thus, TRPV1 is considered a gateway for pain transduction, and a pivotal target for drug intervention in pain syndromes. In addition, due to a widespread tissue distribution of this TRP channel, it may be involved in the etiology of other human pathologies or disorders (Avelino et al. 2002; Inoue et al. 2002).

TRPV1 sensitization by inflammatory conditions is produced through two distinct, but complementary mechanisms, namely: (i) covalent modification of the channel by protein kinase A (PKA) and/or protein kinase C (PKC) phosphorylation (Bhave et al. 2003; Tominaga et al. 2001; Varga et al. 2006; Vellani et al. 2001); and, (ii) rapid recruitment of a vesicular population of TRPV1 channels to the neuronal surface through a Ca^{2+} -dependent, SNARE-mediated exocytosis mechanism in response to pro-algesic agents (Camprubi-Robles et al. 2009; Zhang et al. 2005).

Pharmacologically, TRPV1 is primarily activated by a diverse collection of chemical ligands known as vanilloids (Caterina et al. 2000; Khairatkar-Joshi and Szallasi 2009) (Fig. 2.1). The most known agonist of TRPV1 is capsaicin, the pungent compound of chili peppers. Resiniferatoxin (RTX), a vanilloid from *Euphorbia resinifera*, is also a potent agonist of the receptor. Furthermore, TRPV1 may also be activated by non-vanilloid compounds, such as allicin, piperine, camphor, olvanil, 2-aminoethoxydiphenylborate (2-APB), and tarantula venom peptide toxins (Bohlen et al. 2010) (Table 2.1). In addition, there is a family of endogenous compounds, referred to as endovanilloids, that also act as agonists of TRPV1 (Van Der Stelt and Di 2004). These compounds may be divided into conjugates of biogenic amines [e.g., N-arachidonoylathanolamine (AEA, anandamide), N-arachidonoyldopamine (NADA), N-oleoylathanolamine (OLEA), N-arachidonoylserine, and various N-acyltaurines and N-acylsalsolinols (Appendino et al. 2008), and oxygenated eicosatetraenoic acids like the lipoxigenase products 5-, 12-, and 15-hydroperoxyeicosatetraenoic acids (5S-, 12S-, 15S-HPETE), their reduced hydroxyl analogs, prostaglandins, and leukotriene B4 (Ahern 2003; Huang et al. 2006; Wang et al. 2005) (Fig. 2.1).

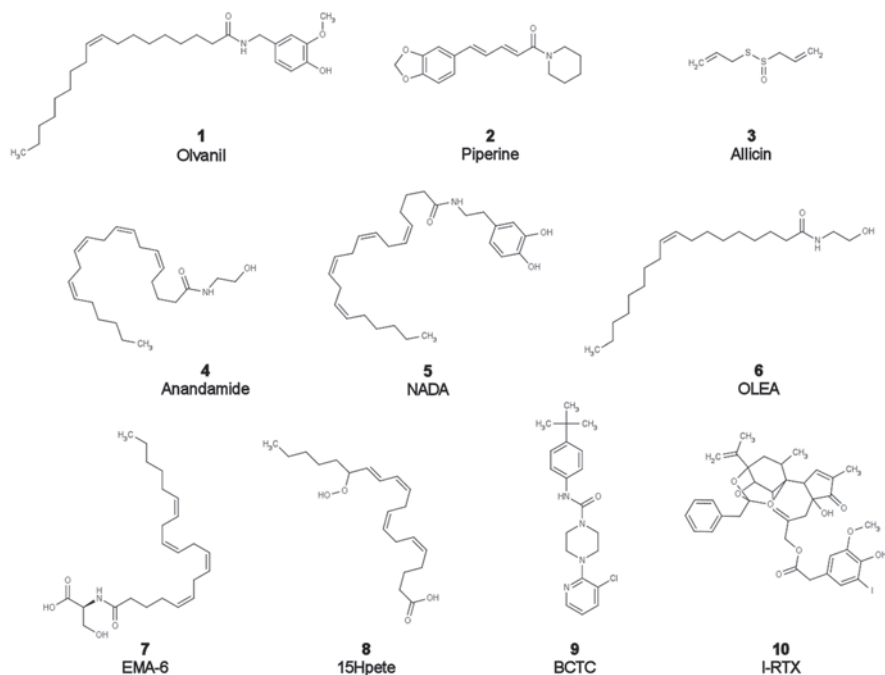


Fig. 2.1 Selected examples of activators (1–8) and inhibitors (9–10) of TRPV1. **1** Olvanil (CID 5311093). **2** Piperine (CID 638024). **3** Allicin (CID 65036). **4** Anandamide (CID 5281969). **5** NADA: N-arachidonoyl dopamine. (CID 5282105). **6** OLEA: N-oleoyl ethanolamine (CID 5283454). **7** EMA-6: N-arachidonoyl serine (CID 10596625). **8** 15-HpETE: 15-hydroperoxy eicosatetraenoic acid (CID 6437084). **9** BCTC (CID 9929425). **10** I-RTX: 5-iodoresiniferatoxin (CID 16219535)

As expected, the activation of TRPV1 in nociceptors with vanilloids causes a burning pain sensation and irritation. Paradoxically, capsaicin has been in use for many years as anti-nociceptive compound in peripheral neuropathies (e.g., post-herpetic neuralgia, neuropathy, mastectomy, amputation and skin cancer). Capsaicin is used as an analgesic, because in addition to activate the channel, it also induces its desensitization. Furthermore, the repetitive application of the vanilloid produces a rundown of channel activity known as tachyphylaxia that results in a strong anti-nociceptive effect (Knotkova et al. 2008). This analgesia may be accompanied by reversible and/or irreversible loss of the capsaicin sensitive C-fibers (Hiura 2000).

Although TRPV1 agonists may have some therapeutic application, their low in vivo activity, along with their poor bioavailability and secondary effects has limited their development as anti-nociceptives, and promoted the research into the design of potent antagonists that display higher therapeutic index. The efforts in developing TRPV1 antagonists have been concentrated in obtaining both competitive and non-competitive (including uncompetitive) inhibitors (Planells-Cases et al. 2003; Szallasi and Appendino 2004). Uncompetitive antagonists acting as open channel

blockers are activity-dependent blockers that preferentially bind to over-activated receptors, with minimal interaction with the physiologically working channels. Accordingly, they are supposed to display lower side-effects than conventional antagonists.

Among the competitive TRPV1 antagonists (Fig. 2.1), capsazepine was the first identified, although with poor in vivo activity (Bevan et al. 1992; Walker et al. 2003). A vanilloid with better therapeutic potential is 5-iodo-RTX, a potent TRPV1 antagonist ($IC_{50}=3.9$ nM) (McDonnell et al. 2002; Wahl et al. 2001). This compound produced notable analgesic activity in vivo and it is currently under clinical studies.

The family of competitive antagonists grew tremendously thanks to the contribution of pharmaceutical companies that established strong drug discovery programs for TRPV1 channels. As a result, ultra-high affinity synthetic antagonists were discovered for analgesic drug development. However, most of the clinical trials for these compounds had to be cancelled in Phase I because the indiscriminate blockade of TRPV1 channels with these compounds resulted in significant hyperthermia in humans, suggesting that this receptor also plays a pivotal role in core body temperature (Gavva et al. 2008).

The first non-competitive TRPV1 antagonist was the trinuclear polyamine complex, ruthenium red that was followed by arginine-rich peptides, and peptidomimetic compounds such as peptoids DD00069 and DD01050 (Garcia-Martinez et al. 2002, 2006). All these compounds resulted in unacceptable in vivo side effects and toxicity that prevented their clinical development. Recently, an uncompetitive antagonist, based in a triazine scaffold (triazine 8aA) that block TRPV1 channel by an activity-dependent mechanism was reported (Vidal-Mosquera et al. 2011). Triazine 8aA showed a strong voltage-dependent TRPV1 blockade by inhibiting at negative membrane potential, a hallmark of open-channel blockers. This compound holds promise for therapeutic development, although in vivo activity in pain models has not been yet reported.

Allosteric modulators of TRPV1 activity are another class of non-competitive antagonists. These compounds interfere with the allosteric mechanism that gates the channel. Structure-function analysis of TRPV1 channels demonstrated that the intracellular TRP domain, a highly conserved region adjacent to the receptor internal gate (Venkatachalam and Montell 2007), is essential for subunit tetramerization and allosteric activation (Garcia-Sanz et al. 2004, 2007). Thus, this protein interface could be used as an allosteric site to modulate channel function. Indeed, compound TRP-p5, a palmitoylated 13-mer peptide patterned after the N-terminus region of the TRP domain, displays in vitro and in vivo inhibitory activity (Valente et al. 2011). This finding is proof-of-concept that allosteric modulators such as TRPducins represent another family of non-competitive antagonists that could be developed therapeutically as anti-nociceptives.

A complementary approach to reduce the inflammatory sensitization of TRPV1 has been to interfere with the recruitment of the channel to the neuronal surface. This strategy has proven that blockers of neuronal exocytosis such as compound DD04107 display analgesic activity (Ponsati et al. 2012). In vitro experiments with DD04107 showed that it blocked the inflammatory over expression of TRPV1

channels to the plasma membrane (Camprubi-Robles et al. 2009). In vivo, this compound displays long-lasting anti-nociceptive activity against inflammatory and neuropathic pain, without apparent side effects, demonstrating that acting on the TRPV1 signalplex may be a valuable pharmacological strategy (Ponsati et al. 2012). This compound is being developed clinically.

2.3 TRPV2

At variance with TRPV1 channels, the pharmacology of its close homologue TRPV2 is still in its infancy (Peralvarez-Marin et al. 2013). This non-selective Ca^{2+} channel is also present in the peripheral nervous system and co-localizes with TRPV1 in a subset of nociceptors (Liapi and Wood 2005). The physiological role of this TRP channel is yet elusive. Initially was considered a thermoTRP channel that activated at 52 °C, and also responded to hypotonicity (Caterina et al. 1999; Muraki et al. 2003). However, these are still highly debated functions (Park et al. 2011; Peralvarez-Marin et al. 2013), thus requiring further investigation, including the discovery of agonists and antagonists that could be used as pharmacological tools.

The identification of specific TRPV2 modulators is, surprisingly, inexistent, probably due to the species-specific pharmacology coupled with problems in developing stable recombinant cell lines due to cytotoxic effects of TRPV2 expression (Penna et al. 2006). Several chemical compounds have been shown to modulate TRPV2, however, virtually all of them are non-specific (Table 2.1 and Fig. 2.2). Indeed, TRPV2 is activated by general TRP channel agonists, such as 2-aminoethoxy-diphenyl borate (2-APB), probenecid, lysophospholipids, and cannabinoids (Juvín et al. 2007; Monet et al. 2009; Qin et al. 2008). However, the response to these ligands is low and variable and quite species-dependent (Neeper et al. 2007).

To date, only general blockers such as ruthenium red and trivalent cations (La^{3+} and Gn^{3+}) (Table 2.1), have been described as blockers of TRPV2 (Lefler et al. 2007). In addition, the potassium channel blockers tetraethylammonium (TEA), 4-aminopyridine (4-AP), and 1-(2-(trifluoromethyl)phenyl)imidazole are also able to block TRPV2 currents (Vriens et al. 2009). Other reported inhibitors are SKF96365, amiloride, and Tranilast, an antiallergic drug (Juvín et al. 2007; Mihara et al. 2010) (Fig. 2.2).

2.4 TRPV3

TRPV3 is a non-selective Ca^{2+} channel that plays a pivotal role in various physiological processes in the skin and hair follicles. This channel displays a moderate sequence homology to TRPV1. TRPV3 is mainly located in keratinocytes and epithelial cells (Nilius and Owsianik 2011; Valdes-Rodriguez et al. 2013), and marginally in sensory neurons (Nilius et al. 2014). This TRP channel is a polymodal receptor

Table 2.1 Representative modulators of depicted TRP channels

Ion channel	Activators	Representative blockers
TRPV1	Capsaicin, resiniferatoxin, olvanil, piperine, eugenol, camphor, 2-APB, allicin, anandamide, NADA, OLEA, N-arachidonolylserine 5S-, 12S-, 15S-HPETE, prostagalandine, leukotriene B4	Capsazepine, ruthenium red, DD01050, 5-iodo-RTX, Triazine 8aA, TRP-p5
TRPV2	2-APB, probenecid, lysophospholipids, cannabinoids	Ruthenium red, La ³⁺ , Gn ³⁺ , TEA, 4-aminopyridine, 1-(2-(tri-fluoromethyl)phenyl) imidazole, SKF96365, amiloride, Tranilast.
TRPV3	2-APB, 17(R)-resolvin D1, PIP ₂ , diphenylboronic anhydride, farnesyl pyrophosphate camphor, carvacrol, eugenol, menthol, thymol, borneol, cresol, carveol, gerianool, propofol, linalool, incensole, citral	Ruthenium red, icilin, isopentenyl pyrophosphate chromane-, fused pyrimidine-, fused pyrimidinones-, chromanone- and fused imidazole-derivatives
TRPV4	Endocannabinoids, arachidonic acid metabolites, nitric oxide, diacylglycerol, bisandrographolide A, 4 α PDD phorbol derivatives, GSK1016790A, RN-1747	RN-1734
TRPC5	Thioredoxin, lysophosphatidylcholine, lanthanides, genistein, diadzein	SKF-96365, BTP-2, flufenamic acid, chlorpromazine, W-13, calmidazolium, W-7, 2-APB, ML-7, ML-9
TRPM3	Pregnenolone sulphate, dihydro-D-erythro-sphingosine, N,N-dimethyl-D-erythro-sphingosine, dihydropyridine nifedipine	2-APB, Gd ³⁺ , rosiglitazone, troglitazone, mefenamic acid, cholesterol, naringenin, hesperetin
TRPM8	Menthol, icilin, geraniol, D3263	AMTB, JNJ41876666, BCTC, Thio-BCTC, clotrimazole, econazole, SKF-96365
TRPA1	Allyl isocyanate, cinnamaldehyde, allicin, nifedipine, chlorpromazine, auranofin, clotrimazole, clioquinol, apomorphine, glibenclamide, BCTC	HC-030031, GRC-17536, A-967079, piperazineurea, N-1-Alkyl-2-oxo-2-aryl amide, 1,8-cineole, chlorpromazine, toxin ProTx-I

activated by non-painful temperatures (Peier et al. 2002a; Smith et al. 2002; Xu et al. 2002), and chemical stimuli (Xu et al. 2006a), including natural irritants and synthetic ligands (Xu et al. 2006a), and endogenous compounds, some of them involved in the downstream inflammatory cascade (Doerner et al. 2011; Sherkheli et al. 2009). Stimulation of TRPV3 releases inflammatory mediators from keratinocytes including ATP, prostaglandin E2 and IL-1, which supports its contribution to pain transduction and inflammatory signaling. Indeed, in certain human disease states there are changes in the expression of TRPV3, such as an increase in painful breast tissue (Matta et al. 2008), or a decrease in keratinocytes in diabetic neuropathy (Facer et al. 2007).

Some evidence points to phosphatidyl inositol-4,5-bisphosphate and 17(R)-resolvin D1 as putative in vivo modulators of TRPV3 (Bang et al. 2012; Doerner et al. 2011) (Table 2.1). A role of 17(R)-resolvin D1 as potential analgesic mediated by TRPV3 has been described, although a direct evidence is still missing (Bang et al.

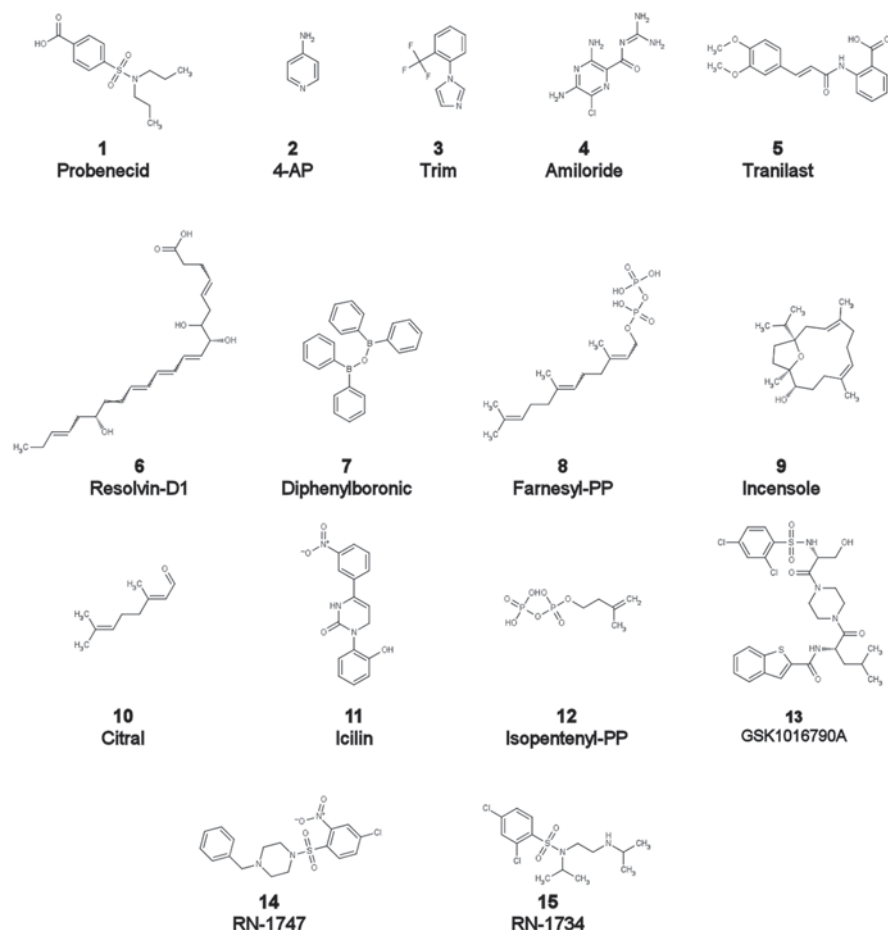


Fig. 2.2 Selected examples of TRPV2-4 effectors. TRPV2 activators (1) and inhibitors (2–5). TRPV3 activators (6–10) and inhibitors (11–12). TRPV4 activators (13–14) and inhibitors (15). **1** probenecid (CID 4911). **2** 4-AP: 4-aminopyridine (CID 1727). **3** Trim: 1-(2-(trifluoromethyl) phenyl) imidazole (CID 1359). **4** Amiloride (CID 16231). **5** Tranilast (CID 5282230). **6** Resolvin-D1: 17(R)-resolvin D1 (CID 71434077). **7** Diphenylboronic anhydride (CID 596810). **8** Farnesyl pyrophosphate (CID 44134714). **9** Incensole (CID 44583885). **10** Citral (CID 638011). **11** Icilin (CID 161930). **12** Isopentenyl pyrophosphate (CID 1195). **13** GSK1016790A (CID 23630424). **14** RN-1747 (CID 5068295). **15** RN-1734 (CID 3601086)

2012). Similarly, TRPV3 has been related with the production of nitric oxide via a nitrite independent pathway (Miyamoto et al. 2011). Furthermore, farnesyl pyrophosphate and isopentenyl pyrophosphate, intermediates of the melanovate pathway, are activator and inhibitor respectively, suggesting a fine-tuning of TRPV3

function (Bang et al. 2010; 2011). Alfa-hydroxy acids are proton donors commonly used in cosmetics to produce skin exfoliation mediated by TRPV3 activation (Cao et al. 2012).

The pharmacology of the TRPV family is far from simple, and TRPV3 is not an exception (Table 2.1 and Fig. 2.2). 2-APB also activates TRPV3 (Chung et al. 2004; Hu et al. 2004, 2009). Prolonged exposure of TRPV3 to 2-APB induced sensitization (Sherkheli et al. 2009). Structurally related 2-APB compounds such as diphenylboronic anhydride also act as potent TRPV3 agonists (Chung et al. 2005).

Natural aromatic monoterpenes, such as camphor, carvacrol, eugenol, menthol, thymol, as well as borneol, cresol, and others are an additional class of TRPV3 ligands (Moqrich et al. 2005; Vriens et al. 2009; Xu et al. 2006a). Camphor is a weak agonist for TRPV3 that activates currents only at concentrations of 10 mM. Carvacrol is responsible for arterial vasodilation by activating TRPV3 channels in the endothelium (Earley et al. 2010), which may account for some of their attributed cardioprotective effects. In addition to camphor and carvacrol, thymol and eugenol have also been shown to enhance the temperature response of TRPV3 (Macpherson et al. 2006; Xu et al. 2006a).

Non-aromatic monoterpenes such as carveol and derivatives (monocyclic), or geraniol, propofol and linalool (acyclic) display strong TRPV3 agonism (Vogt-Eisele et al. 2007). Incensole and incensole acetate are diterpenic cembrenoids found in incense (*Boswellia papyrifera*) potently activate TRPV3. The traditional use of these natural products is related to anti-inflammatory effects through the activation of TRPV3 in the skin. Interestingly, incensole acetate produces anxiolytic and antidepressive effects in mice (Moussaieff and Mechoulam 2009; Paul and Jauch 2012). Citral, a bioactive component of lemongrass is also an agonist of TRPV3 (Stotz et al. 2008), adding to the list of compounds acting on this channel (Fig. 2.2).

Cannabinoids such as cannabidiol or delta-9-tetrahydrocannabinol modulate nonspecifically TRPV3. Other derivatives such as cannabigerovarin or cannabigerolic desensitize TRPV3 (De Petrocellis et al. 2012). Active research is necessary in this field because, interestingly, the activation of TRPV3 by these compounds may contribute to their described *in vivo* activity (Anand 2003; Galeotti et al. 2001; Santos and Rao 2001; Umezu et al. 2001; Xu et al. 2005a).

TRPV3 antagonists include the non-specific ruthenium red, that blocks all TRPV family member at negative potentials (Vennekens et al. 2008). The compound icilin, which is a strong agonist of TRPM8 channel, is an inhibitor of TRPV3 at low doses (Sherkheli et al. 2012). Novel inhibitors are under study and have promising analgesic effects, which further suggests the involvement of TRPV3 in pain transduction (Reilly and Kym 2011). Several pharmaceutical industries have reported strong and selective TRPV3 antagonists including series of chromane-, fused pyrimidine-, fused pyrimidinones-, chromanone- and fused imidazole-derivatives (Ferrer-Montiel et al. 2012). Some of these antagonists are currently under clinical studies to treat human pain conditions.

2.5 TRPV4

Transient Receptor Potential Vanilloid 4 (TRPV4) a non-selective Ca^{2+} channel is a homologue of the OSM-9 osmosensory channel first described in *C. elegans*. TRPV4 is activated by warm temperatures (27–35 °C) (Guler et al. 2002; Liedtke et al. 2000), and is sensitive to cell swelling and shear stress (Gao et al. 2003; Kohler et al. 2006; Loukin et al. 2010; Strotmann et al. 2000). Functions include temperature monitoring in skin keratinocytes, osmolarity sensing in the kidney (Pochynyuk et al. 2013), and shear stress detection in blood vessels, which indicates that TRPV4 functions as a putative mechanosensor (Nilius et al. 2003a, b), and is involved in nociception (Alessandri-Haber et al. 2005, 2006). It has been reported that TRPV4 may be activated by hypotonic solutions, and by mechanical forces in membrane patches (Loukin et al. 2009). TRPV4 may contribute to development of mechanical hyperalgesia after inflammation and injury (Alessandri-Haber et al. 2006). This channel is expressed in several tissues, including primary sensory neurons (Alvarez et al. 2006; Birder et al. 2007; Guler et al. 2002; Pochynyuk et al. 2013; Strotmann et al. 2000; Tabuchi et al. 2005; Watanabe et al. 2002b; Yang et al. 2006).

TRPV4 is activated by endogenous chemical ligands, such as endocannabinoids, arachidonic acid metabolites and nitric oxide (Birder et al. 2007) (Table 2.1 and Fig. 2.2). Phorbol esters that do not activate PKC, mediate TRPV4 heat responses (Watanabe et al. 2002a). TRPV4 sensitivity to osmotic and mechanical stimuli may depend on phospholipase A2 activation and the generation of arachidonic acid metabolites (Fernandes et al. 2008; Liedtke et al. 2000; Strotmann et al. 2000; Vriens et al. 2004). Furthermore, TRPV4 is activated by hypotonicity, diacylglycerol, and PKC-activating phorbol esters (Watanabe et al. 2002a, b, 2003).

Natural plant extracts (Klausen et al. 2009), bisandrographolide A (Smith et al. 2006) and synthetic compounds, such as a phorbol derivative (Birder et al. 2007), or GSK1016790A (Thorneloe et al. 2008) also activate TRPV4 channels. In addition, small molecules such as compound RN-1747 was also found to be a TRPV4 agonist (Vincent et al. 2009) (Table 2.1 and Fig. 2.2).

TRPV4 antagonism is being considered for inflammatory and neuropathic pain treatment (Vincent and Duncton 2011). However, selective TRPV4 antagonists have not been described appropriately. Ventilator-induced lung injury has emerged as a potential indicator for TRPV4 antagonists (Jin et al. 2011) (Table 2.1). The small molecule RN-1734 2,4-Dichloro-N-isopropyl-N-(2-isopropylaminoethyl)benzenesulfonamide was observed to inhibit ligand- and hypotonicity-activated TRPV4 (Vincent et al. 2009). In addition, the compound showed selective properties for TRPV4 over other TRPs such as TRPV1, TRPV3 and TRPM8, being a valuable pharmacological tool for TRPV4 studies (Vincent et al. 2009).

TRP Channels in Sensory Transduction

Madrid, R.; Bacigalupo, J. (Eds.)

2015, X, 234 p. 33 illus., 23 illus. in color., Hardcover

ISBN: 978-3-319-18704-4