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REVIEW

TRP channels: potential drug target for neuropathic pain

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Abstract Neuropathic pain is a debilitating disease which affects central as well as peripheral nervous system. Transient receptor potential (TRP) channels are ligand-gated ion channels that detect physical and chemical stimuli and promote painful sensations via nociceptor activation. TRP channels have physiological role in the mechanisms controlling several physiological responses like temperature and mechanical sensations, response to painful stimuli, taste, and pheromones. TRP channel family involves six different TRPs (TRPV1, TRPV2, TRPV3, TRPV4, TRPM8, and TRPA1) which are expressed in pain sensing neurons and primary afferent nociceptors. They function as transducers for mechanical, chemical, and thermal stimuli into inward currents, an essential first step for provoking pain sensations. TRP ion channels activated by temperature (thermo TRPs) are important molecular players in acute, inflammatory, and chronic pain states. Different degree of heat activates four TRP channels (TRPV1–4), while cold temperature ranging from affable to painful activate two indistinctly related thermo TRP channels (TRPM8 and TRPA1). Targeting primary afferent nociceptive neurons containing TRP channels that play pivotal role in revealing physical stimuli may be an effective target for the development of successful pharmacotherapeutics for clinical pain syndromes. In this review, we highlighted the potential role of various TRP channels in different types of neuropathic pain. We also discussed the pharmacological activity of naturally and synthetically originated TRP channel modulators for pharmacotherapeutics of nociception and neuropathic pain.

Keywords TRP channels · Neuropathic pain · Pharmacotherapy · Drug target

Introduction

Neuropathic pain (NP), according to the International Association for the Study of Pain (IASP), is "pain initiated or caused by a primary lesion or dysfunction in the nervous system". Neuropathic pain is debilitating heterogeneous consequence caused by destruction of nerves (in the central or peripheral or somatosensory nervous system) (Treede et al. 2008). Neuropathic pain can be inherent and usually depicted as shooting, burning, or stabbing. Neuropathic pain involves positive and negative sensory symptoms concomitant in neuropathic pain (Baron 2006). Negative symptoms comprise different somatosensory functional deficits, such as tactile hypoesthesia or anesthesia, thermal hypoesthesia, pinprick hypoalgesia, and loss of vibratory sensation, are uncomfortable but not painful. Instinctive positive symptoms are paroxysmal and ongoing superficial pain, paresthesia, and dysesthesia, and stimulus evoked positive symptoms include allodynia and hyperalgesia (Baron 2006).

TRP channels are ion channel family members involved in different physiological and pathological conditions, such as neuropathic pain, pulmonary hypertension, asthma, parkinsonism, and prostate cancer (Nilius et al. 2007). These are of six different types, such as TRPV1, TRPV2, TRPV3, TRPV4, TRPM8, and TRPA, which have been expressed in primary afferent nociceptors and pain sensing neurons, act as transducers for chemical, thermal, and

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mechanical stimuli (Clapham 2003; Corey 2003; Montell et al. 2002). In this article, we discuss recent developments associated with different types of TRP channels as potential targets for pharmatherapeutics of neuropathic pain.

TRP channels family

TRP channels were discovered in 1969 as mutant Drosophila photoreceptors (Cosens and Manning 1969). Process of phototransduction in the fruit fly, *Drosophila melanogaster*, comprises membrane cation channels activation leading to a depolarizing current. Activation of *Drosophila* photoreceptors, i.e., light-sensitive G protein-coupled receptor *rhodopsin*, results in the stimulation of phospholipase C-β (PLC-β). The light-induced current resolving components escorted to identification of a *Drosophila* mutant exhibiting a transient LIC in response to light, in comparison to the sustained LIC in wild-type flies, and mutant strain was termed *trp*, for transient receptor potential. *Trp gene* mutations headed to a disruption of a Ca^{2+} entry channel in the photoreceptors, representing that TRP, the protein encoded by the *trp* gene, forms whole or part of a Ca^{2+} influx channel (Nilius et al. 2007). TRP channels are Ca^{2+}-permeable non-selective cation channels.

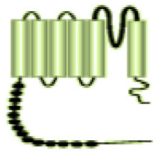
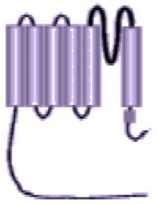
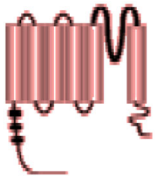
Mammalian TRP channels are classified into different subfamilies (as shown in Table 1): TRPC (canonical), TRPV (vanilloid), TRPM (melastatin), TRPP (polycystin), TRPML (mucolipin), and TRPA (ankyrin) (Caterina 2007). All TRP subunits have six transmembrane domains (TMD), a pore-forming loop (between 5th and 6th transmembrane segments) and having widely varying intracellularly located amino (N) and carboxyl (C) terminal in length (Clapham 2003; Vriens et al. 2004a). Mammalian TRP channels are with low-sequence homology, and have different modes of activation (mechanical stimulation, temperature, chemical compounds, osmolarity, lipids, light, oxidative stress, acid, and pheromones), regulation (glycosylation, transcription, phosphorylation, and alternative splicing), broad tissue distribution (at least one member of the family present virtually in all cells), ion selectivity, and physiological functions (Levine and Alessandri-Haber 2007). After TRPV1 cloning, some other TRPs have been depicted in dorsal root ganglia (DRG), such as TRPV2, TRPV3, TRPV4, TRPA1, and TRPM8, which act as sensory transducers and play an important role in the generation of pain sensations evoked by thermal, mechanical, and chemical stimuli. In Table 1, TRPV1, TRPV2, TRPV3, and TRPM8 are thermoreceptors, and TRPV4 and TRPA1 referred as mechanoreceptors, while TRPV1, TRPV3, TRPM8, and TRPA1 are known as chemoreceptors, respectively, receptive to capsaicin and endocannabinoids, camphor, menthol, mustard, and cinnamon oil (Bandell et al. 2004; Jordt et al. 2004).

TRPV1

TRPV1 is a polymodal receptor named as Vanilloid receptor 1(VR1) whose invertebrate families are necessary to sensory transduction (mechanosensation, osmosensation, phototransduction, and thermosensation) and in mammals, it is activated by heat and protons, and leads to the influx of cations which depolarize the cell for action potential generation (Vriens et al. 2004a). TRPV1 was predominantly found in a subpopulation of small-to-medium-diameter neurons in dorsal root and trigeminal ganglia. TRPV1 plays an amenable role in thermal and chemical hyperalgesia in a model of diabetic neuropathy (Hong and Wiley 2005; Kamei et al. 2001). They play role by altered cell-specific expression like by decrease of TRPV1 protein expression in C-fibers paralleled by an increase in A-fibers which coupled to an increase in its function (reallocation of channels to cell-surface plasma membrane and/or increase of TRPV1 phosphorylation coupled to oligomerization and impaired desensitization) (Levine and Alessandri-Haber 2007).

TRPV1 is activated by capsaicin, thermal heat ($\geq$43 °C), low pH ($<$5.9) (Caterina et al. 2000; Tominaga et al. 1998), camphor (Xu et al. 2005a), allicin (Macpherson et al. 2005), nitric oxide (Yoshida et al. 2006), spider toxins (Siemens et al. 2006), vanilloids (Caterina and Julius 2001), protons (Caterina and Julius 2001), and proalgesic substances (Julius and Basbaum 2001), and modulated and potentiated by extracellular cations and ethanol, respectively. TRPV1 can be sensitized and up-regulated during inflammation and injury. In several conditions, TRPV1 activation demonstrated as different models of pain like in inflammatory conditions and temperature threshold of activation is reduced causing the channel to be active at normal body temperatures. TRPV1 sensitization depends on phosphorylation of TRPV1 by protein kinase A (PKA) and protein kinase C (PKC). TRPV1 activation-associated pain conditions are inflammatory thermal hypersensitivity, acute thermal pain, post-herpetic neuralgia, constriction-type nerve injury, trigeminal neuralgia, diabetic peripheral neuropathy, headache and cardiac pain, pain arising from GI diseases, cluster, lung diseases, cancer pain, and migraine (Cortright and Szallasi 2004; Premkumar 2010; Premkumar and Sikand 2008; Szallasi 2006; Szallasi and Appendino 2004; Szallasi et al. 2007). TRPV1 channel is incriminated in a variety of human diseases, including gastrointestinal reflex disease, osteoarthritis, inflammatory disorders of the airways, and urinary bladder (Groneberg et al. 2004; Matthews et al. 2004; Nilius et al. 2005).

Table 1 Mammalian TRP channel involved in neuropathic pain

TRP family	Channel name	Temperature threshold	Distribution	Regulatory mechanism	Agonist	Antagonist	Pathophysiological role	Expression in different models
TRPA 	TRPA1	≤18 °C	DRG, fibroblast, hair cells	(+) PLC_{β}	Cannabinoids, mechanical stimulus mustard oil and cinnamaldehyde	Mecamylamine, camphor (at high dose)	Neuropathic pain, nociception, allodynia, cold hyperalgesia	Increased level in chronic constriction injury (CCI) model
TRPM 	TRPM5	–	Taste tissue, small intestine, lungs, liver	(+) Intracellular Ca^{++}, PIP_2, $PLC_{\beta}2$	Linoleic acid	–	Impaired glucose tolerance	–
	TRPM8	23–28 °C	DRG, TG, prostate	(+) PIP_2, (−) Intracellular acidification	Eucalyptol, menthone, spearmint, menthol, and icilin	PF-05105679, and capsazepine	Neuropathic pain, cold allodynia and prostate cancer	–
TRPV 	TRPV1	≥43 °C	Dorsal root ganglia (DRG), trigeminal ganglia (TG), urinary bladder	(+) PKC,PKA,PLC,PLA_2/LOX, NGF, PGE_2, and ATP	Capsiacin, triprenylphenols, gingerol, gingenosides, nicotine, anandamide, ethanol, endocannabinoids, spermidine, resiniferatoxinputrescine and arachidonic acid metabolites(PGE_2, 12-HPETE)	Capsazepine, yohimbine, 2-APB (at low dose), ruthenium red, methoctramine	Neuropathic pain and chronic pain, thermal and mechanical hyperalgesia	Increased level in Spared nerve ligation (SNL) model
	TRPV2	>52 °C	DRG, spinal cord (SC), brain, spleen, intestine	(+) translocation (by IGF-1)	2-APB (higher dose)	2-APB (at low dose)	Inflammatory pain, neuropathic pain, thermal and mechanical hyperalgesia	–
	TRPV3	>30–39 °C,	DRG, TG, SC, keratinocytes, brain, tongue	(+) 2-APB	Camphor	2-APB (at low dose)	Pain and inflammation, thermal and mechanical hyperalgesia	–
	TRPV4	>25 °C	DRG, TG, SC, brain keratinocytes, tonsil, kidney, spleen, lungs, testis,endothelin, heart and inner-hair cells	(+) PLA_2/cytochrome P450,Src,PGE_2	Noxious mechanical stimulus, arachidonic acid metabolites, hypotonicity and endocannabinoids	2-APB (at low dose)	Neuropathy, thermal and mechanical hyperalgesia and nociception	–

The contribution of TRPV1 in inflammatory, nociceptive, and neuropathic pain created an interest in discovery of specific vanilloid receptor antagonists. TRPV1 is involved in heat evoked pain, thermal hyperalgesia, and deep tissue pain in CNS and primary terminals of primary afferents. TRPV1 can be activated by noxious heat and its threshold temperature (≥43 °C) lies close to sense as painful for humans. TRPV1-null mice exhibited reduced nocifensive responses to acute thermal stimuli arguing for the role of TRPV1 in transducing thermal pain in vivo (Caterina et al. 2000; Davis et al. 2000; Levine and Alessandri-Haber 2007). TRPV1 is involved in the hyperalgesia after the injection of inflammatory mediators, such as bradykinin, adenosine triphosphate (ATP), nerve growth factor (NGF), and protease (Caterina et al. 2000; Chuang et al. 2001; Davis et al. 2000). TRPV1 acts as a crucial molecular site of nociceptor sensitization where activity of both a noxious stimuli (heat) and inflammatory mediators is required for nociceptor activation. TRPV1 involves in nociception in deep tissues, such as musculoskeletal and visceral tissues. Deep tissues pathological conditions mainly produce mechanical hyperalgesia rather than thermal hyperalgesia, and a number of deep tissue pain models have been shown the involvement of TRPV1 (Chung et al. 2011). TRPV1 is necessary for sensitization of afferent fibers of mouse colon by inflammatory mediators (Jones et al. 2005; Miranda et al. 2007; Ravnefjord et al. 2009).

TRPV1 plays a critical role in joint pain in an arthritis model and increased number of sensory neurons expressing TRPV1 has been found in rats after induction of arthritis (Fernihough et al. 2005). TRPV1 is implicated in pain associated with bone cancer and the movement-induced nocifensive behaviour in bone cancer model is ameliorated by specific TRPV1 antagonists (Niiyama et al. 2007). The number of TRPV1-expressing neurons in DRG was found to be increased in experimental bone cancer. TRPV1 acts as a transducer of thermal stimuli at the peripheral terminal of primary afferents and also expression of TRPV1 has been demonstrated in the spinal cord, mainly at the lamina I and II of the superficial dorsal horn area (Guo et al. 1999; Valtschanoff et al. 2001). TRPV1 is activated by central branches of primary afferents to release excitatory amino-acid glutamate and produces excitatory synaptic transmission in superficial dorsal horn (Pan and Pan 2004; Sikand and Premkumar 2007; Yang et al. 1999, 1998). Strong correlation between therapeutic efficacy and CNS penetrability of TRPV1 antagonists tells that centrally located TRPV1 blockade is also involved in the antinociceptive effects of TRPV1 antagonists.

TRPV2

TRPV2 was discovered as structural homologue of TRPV1 with 50 % amino-acid identity and originally named as vanilloid receptor-like protein 1 (VR-L1) (Caterina et al. 1999). Higher temperature (~52 °C), 2-aminoethoxyphenyl borate (2-APB) at higher dose, inflammation, osmotic stimuli, and mechanical stretch are activators of TRPV2, but it is insensitive to capsaicin (Caterina et al. 1999; Jordt et al. 2004; Muraki et al. 2003). The growth factor (insulin-like growth factor-I) and PI3-kinase signalling pathways enhance TRPV2 activity. TRPV2 is usually expressed in neuronal and non-neuronal cells, Aδ and Aβ fibers of DRG, trigeminal ganglia (TG), and nodose ganglion (NG) (Lewinter et al. 2004; Stokes et al. 2005; Wainwright et al. 2004). The expression of TRPV2 in neurons innervating the larynx, bladder, and intestine suggests its role in sensory functions of internal organs (Kashiba et al. 2004) and is activated by 2-aminoethoxydiphenylborate (2-APB) at higher concentration. TRPV2 is expressed throughout the spinal cord, including laminae III and IV, suggesting a role other than nociception (Caterina and Julius 1999; Lewinter et al. 2004). TRPV2 has been distributed in neurotropin-3-dependent subpopulation of DRG neurons and its protein level release beyond the normal level following inflammation and has ability to hetromultimerize and ability to be activated by 2-APB indicates its role in pain associated with inflammation and neuropathy (Tamura et al. 2005). Fewer studies related to pain that focuses on TRPV2 because of its very high heat threshold as well as differential distribution.

TRPV3

TRPV3 shows 40–50 % homology with TRPV1 and is activated by warm temperature (≥34 °C). They are having ability to show augmented responses to higher noxious thermal stimuli and increased current following repetitive heat stimulation (Peier et al. 2002b; Smith et al. 2002; Xu et al. 2002). These are strongly activated and sensitized by cloves, camphor, oregano, and irritants extracted from thyme (Xu et al. 2006). Initially, TRPV3 exhibited to be expressed only in keratinocytes, while some other studies have also shown to be expressed in sensory neurons (Facer et al. 2007). TRPV3 is found in TG, DRG, and NG neurons, keratinocytes, and certain regions of the brain and have a role in thermoregulation (Moqrich et al. 2005). It is suggested that TRPV1 and TRPV3 receptors act as a potential therapeutic target for the treatment of pain and inflammation.

TRPV4

TRPV4 is mechano/osmosensitive channel expressed in many cell types, including sensory neurons and a polymodal receptor involved in nociception and activated by low pH, shear stress, hypotonicity, diacylglycerol (DAG), innocuous

heat with threshold >27 °C, citrate, endocannabinoids, and nitric oxide (Guler et al. 2002; Watanabe et al. 2002). These are mainly present in cochlear hair cells, sensory ganglia (Guler et al. 2002), as well as in cutaneous A and C-fiber terminals and free nerve endings, and suggested a role in mechano-transduction, beyond osmosensation. OSM-9, a homologue of the *C. elegans* osmosensory channel, expressed in cochlear hair cells, sensory neurons, vascular smooth muscle cells, hypothalamus, trachea, kidney, keratinocytes, and endothelial cells (Strotmann et al. 2000). Mice lacking functional TRPV4 show normal response to low-threshold mechanical stimuli and noxious heat (Vriens et al. 2004b). Agonists of TRPV4 promote the liberation of the neuropeptides like substance P and calcitonin gene-related peptide (CGRP) from the central projections of primary afferents in the spinal cord. These studies suggest a role of TRPV4 in detection of warm temperature, nociception, and chemically induced hyperalgesia (Grant et al. 2007; Todaka et al. 2004). In TRPV4 knockout mice, the sensitivity of tail to pressure and acidic nociception is diminished as compared with wild-type mice (Suzuki et al. 2003). TRPV4 channels can also act as target for treatment of nociceptive and neuropathic pain.

TRPA1

TRPVA1 is new TRP subfamily member, characterized by the presence of a large number of ankyrin repeat motifs located on the cytosolic amino terminal domain (TRPAnkyrin) (Story et al. 2003), was identified as a protein overexpressed in liposarcoma cell lines (ANKTM1) (Jaquemar et al. 1999). TRPA1 is expressed in the inner ear, lung fibroblast, trigeminal and DRG neurons, motor neurons, postganglionic sympathetic neurons, and neurons of the intestinal myenteric plexus (Corey et al. 2004; Munns et al. 2007; Poole et al. 2011; Smith et al. 2004). TRPVA1 activation by physical stimuli, such as noxious cold (<18 °C) temperatures, mechanical force (Story et al. 2003), by garlic, mustard oil, wintergreen oil, ginger, clove oil, and cinnamon oil leads to induction of acute painful burning or pricking sensation (Bandell et al. 2004; Jordt et al. 2004; Macpherson et al. 2005). It acts as sensor for mechanical stimuli and plays a role in mechanical nociception because of its Drosophila homologue (Xu et al. 2005a). Its involvement in cold allodynia and mechanical hyperalgesia is reported in different behavioural models (Baron 2006; Katsura et al. 2006; Obata et al. 2005) that suggest TRPVA1 as good target for neuropathic pain treatment.

TRPC3 and TRPC6

TRP channel expression in human monocytes is affected by high glucose-induced oxidative stress. TRPC3 and TRPC6 protein expression was enhanced by increased 1-oleoyl-2-acetyl-sn-glycerol induced Ca^{2+} influx, which was blocked by the TRPC channel inhibitor, i.e., 2-aminoethoxydiphenylborane (2-APB) (Wuensch et al. 2010). These may also be act as potential targets for treatment of diabetic neuropathy.

TRPM5, TRPM6, and TRPM7

TRPM5 are present in taste bud tissues and papillae. TRPM6 and TRPM7 supposed to involve in type-2 diabetes mellitus because of their gene variation (Romero et al. 2010). TRPM7 gene variation could play a role in the risk of ischemic stroke.

TRPM8

TRPM8, a cold-sensitive receptor, is known as cold and methanol-activated channel with voltage-dependent gating properties (McKemy et al. 2002; Peier et al. 2002a). It is thermally regulated channel activated in vitro by neurons originating from both TG and DRG (Dhaka et al. 2008). It may be involved in cold-evoked nocifensive responses under temperatures ranging from innocuous cold (26–15 °C) to noxious cold (<15 °C) (McKemy et al. 2002) and by various other chemicals, including eucalyptol, menthone, spearmint, and icilin (Peier et al. 2002a; Tominaga and Caterina 2004). TRPM8 is expressed in a subpopulation of primary afferent sensory pathological conditions. In a chronic constriction injury (CCI) model, the percentage of sensory neurons expressing TRPM8-like immunoreactivity is increased (Xing et al. 2007).TRPM8 is a good target for treatment of cold allodynia, a common feature of neuropathic pain.

TRP channels in neuropathic pain

TRPV1

TRPV1 channels are prominently associated with neuropathic pain as shown by experimental evidences. Desensitization or amputations of TRPV1-positive sensory nerve endings exhibit analgesic effect and make it potential therapeutic target in treatment of neuropathic pain (Haanpaa and Treede 2012; Moran et al. 2011). TRPV1 exhibits Ca^{2+}-dependent desensitization mediated by calmodulin (CaM) which directly binds with calmodulin-binding sites present on several TRP channels (Lambers et al. 2004). TRPV1 shows its expression and function in sensory ganglia in neuropathic pain. Spinal nerve ligation (SNL)-induced nerve injury increases the proportion of TRPV1-expressing IB4-positive DRG neurons and improves

TRPV1 function, resulting in persistent thermal hyperalgesia (Vilceanu et al. 2010). After sciatic nerve transection in rats, TRPV1 at the central terminals of primary afferent neurons in the spinal cord is up-regulated, and augment release of inflammatory neuropeptides like CGRP (calcitonin gene-related peptide), substance P from the presynaptic central terminals along with enhanced glutamatergic neurotransmission, is involved in the neuropathic pain (Kanai et al. 2005; Lappin et al. 2006; Lee and Kim 2007; Spicarova et al. 2011). Activity of TRPV1 enhanced in neuropathic pain, and administration of selective TRPV1 inhibitors allays SNL-induced hyperalgesia and mechanical allodynia (Jhaveri et al. 2005; Urano et al. 2012; Vilceanu et al. 2010; Watabiki et al. 2011).

TRPA1 and TRPM8

TRPA1 and TRPM8 proposed to act as a cold transducer and deliberated as a major candidate for mediating cold allodynia, common feature of neuropathic pain (del Camino et al. 2010; Ji et al. 2008; Knowlton et al. 2011; Obata et al. 2005). TRPA1 function inhibition peculiarly diminishes cold allodynia induced in chronic constriction injury (CCI)-induced neuropathy model of neuropathic pain Chen et al. 2011). Both TRPV1 and TRPA1 are involved in chemotherapy-induced peripheral neuropathy and neuropathic pain. Inhibition of TRPA1 function eradicates both mechanical and cold allodynia induced by cisplatin and oxaliplatin, most commonly used chemotherapeutic agents (Baron 2009; Brederson et al. 2013; Nassini et al. 2011; Zhao et al. 2012). Neuropathy induced by paclitaxel chemotherapy is reported to elicit the release of mast cell tryptase to activate protease-activated receptor 2 (PAR2), which sensitizes TRPV1, TRPV4, and TRPA1 through PLC, PKC, and PKA signalling to initiate neuropathic pain behaviours (Chen et al. 2011) and also enhances the TRPV1 mRNA transcripts and amount of TRPV1 protein in small-to-medium diameter DRG neurons that contribute to neuropathic pain (Hara et al. 2013). Therefore, different TRP channels play a crucial role in the management of neuropathic pain.

Mechanistic involvement of TRP channels in neuropathic pain

Neuropathic pain can be evoked by raising local Ca^{2+} ion concentration at the site of injury or in the spinal cord (Fernyhough and Calcutt 2010) by influx of calcium ions through voltage-dependent Ca^{2+} channels like high-voltage activated or low-voltage activated or transient (T-type) Ca^{2+} channels. When pain impulse transmitted from the periphery to the central nervous system, the nociceptive transmitters like substance P released via exocytosis from the primary sensory terminals present in the spinal dorsal horn, which is regulated by high-threshold voltage-dependent Ca^{2+} channels (Verkhratsky and Fernyhough 2008). Increased responsiveness of the spinal pain transmission is probably due to the increased awareness of the primary afferent neurons, which can results in enhanced neurotransmitter exocytosis through the opening of voltage-dependent Ca^{2+} channels or due to the postsynaptic hyperexcitability in dorsal horn projection neurons, which is possibly induced by enhanced Ca^{2+}-influx through voltage-dependent Ca^{2+} channels (TRP Channels). Oxidative stress-dependent Ca^{2+} over influxes through the TRP channel also has important role in diabetic neuropathic pain (Umeda et al. 2006) and other types of neuropathy (Fig. 1).

TRP channel modulators

TRP channel modulators possess strong pharmacotherapeutic potential for management of neuropathic pain. Natural compounds which act as agonists to modulate TRPV1 channels are capsaicinoids, triprenyl phenols, unsaturated dialdehydesterpenes (Thapsigargin), gingerols, and gingenosides (Calixto et al. 2005) (Table 2).

Capsaicin

It is a TRPV1 modulator that leads to degeneration of a large portion of C-fibers as well as a small portion of Aδ-fibers, resulting in a prolonged analgesic period (in adult and neonatal experimental animals) (Holzer 1991). TRP channel agonists directly gate the channel by reduction of the heat threshold of activation. Persistent exposure of receptor to the agonist in the presence of Ca^{2+} induces channel closure by desensitisation and tachyphylaxis (Szallasi and Blumberg 1999) and also act by phosphorylation of a key residue at the C-terminus of the protein (Bhave and Gereau 2004). Capsaicin is used to diminish pain, due to its ability to desensitize TRPV1. Capsaicin (as 0.025–0.075 % cream preparations) is used for treating pain produced by peripheral neuropathy, osteoarthritis, and rheumatoid arthritis (Brito et al. 2014). Capsaicin desensitises TRP channels and selectively depletes TRPV1-expressing nociceptors due to Ca^{2+} overload (Karai et al. 2004). High-affinity agonists that promote receptor tachyphylaxia and/or nociceptor ablation could be used as efficacious pain relievers. Intrathecal administration of oligodeoxynucleotide antisense for TRPA1 completely repressed the cold hyperalgesia induced by nerve damage in neuropathic pain (Katsura et al. 2006).

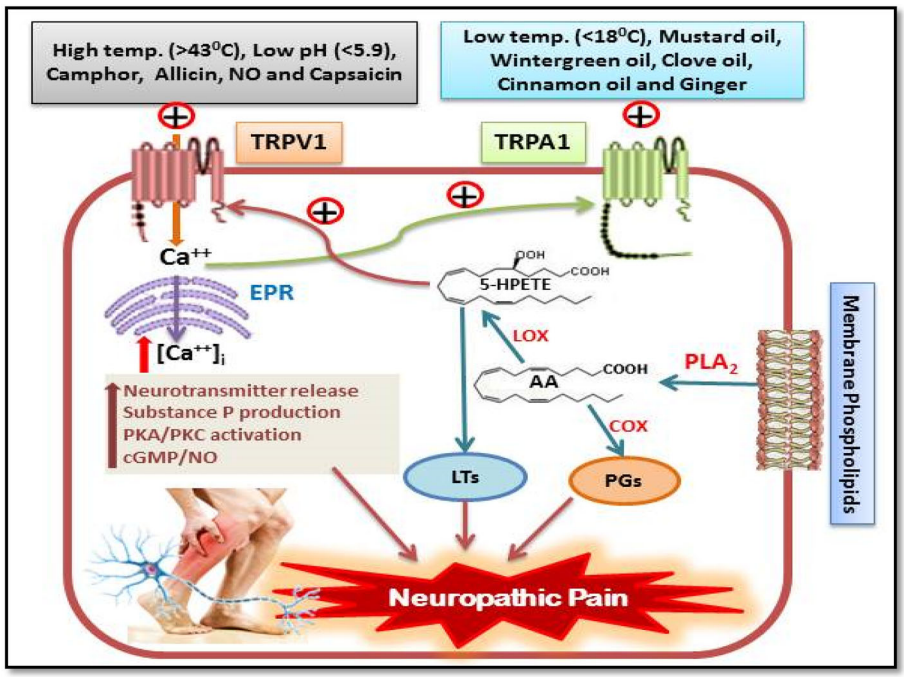


Fig. 1 Schematic representation of Mechanistic pathway involved in neuropathic pain. **a** Role of TRPV1 ant TRPA1: different TRPV1 agonist like capsaicin, camphor, high temperature, low pH, etc., activates the transient type Ca^{2+}-channel to increase the intracellular Ca^{2+} influx in cytosol. This intracellular Ca^{2+} activates TRPA1 channels as well as increase Ca^{2+} concentration in EPR which leads to neurotransmitter release like substance P, activation of PKA/PKC and cGMP/NO pathway which results in progression of neuropathic pain. **b** Role of Arachidonic acid (AA) metabolites: AA metabolites like 5-HETPE also activates TRPV1. Leukotrienes produced by LOX pathway and PGs from COX pathway also involved in neuropathic pain. (Ca^{++}/Ca^{2+} calcium ion, *LTs* leukotrienes, *AA* arachidonic acid, *COX* cyclooxygenase, *LOX* lypooxygenase, *PGs* prostaglandins, PLA_2 phospholipase A_2, *5-HPETE* 5-hydroperoxyeicosatetraenoic acid, *EPR* endoplasmic reticulum)

Camphor

Camphor is a well-known TRPA1 antagonist. It activates TRPV1, TRPV3, and TRPA1 channels at low concentration, but inhibits TRPA1 currents at high concentrations (Xu et al. 2005a).

Mecamylamine

Mecamylamine is a TRPA1 antagonist as well as a non-selective and non-competitive antagonist of the nicotinic acetylcholine receptors (nAChRs) (Bacher et al. 2009) used to treat hypertension and measures cigarette smoke extract (CSE)-evoked vascular endothelial growth factor (VEGF) release.

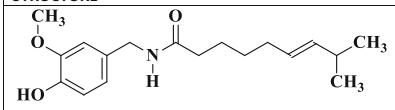
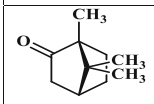
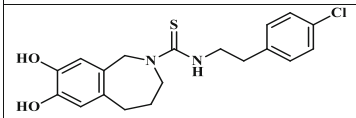
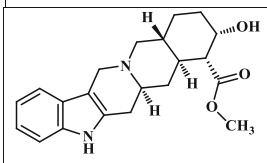
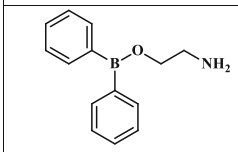
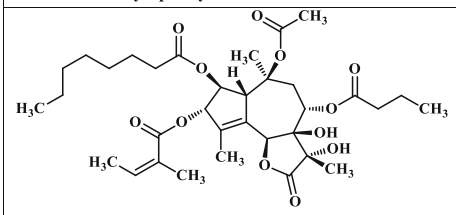
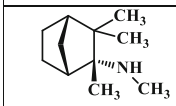
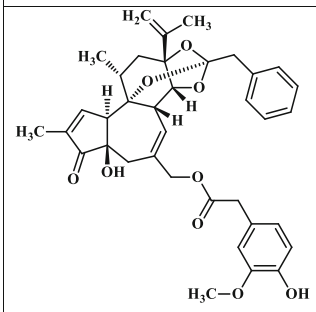
Capsazepine

It blocks painful sensation of heat caused by capsaicin. TRPV1 expression is elevated in uninjured ganglia in nerve injury model and capsazepine allays nerve injury induced hyperalgesia and mechanical allodynia. It acts as TRPM8 antagonist to treat cold allodynia (Behrendt et al. 2004) and inhibits voltage gated Ca^{2+} channels (Docherty et al. 1997) along with nicotinic acetylcholine receptors (Liu and Simon 1997). TRPV1 levels are elevated in visceral sensory afferents in inflammatory bowel disease in humans (Holzer 2004). Analgesic effect of TRPV1 antagonists due to dual (both peripheral and central) action is vital for full analgesic action (Cui et al. 2006). Inflammatory mediators, such as glutamate (acting on metabotropic receptors 5), bradykinin (acting on B_2 receptors), prostaglandins E2 (acting on EP receptors), or NGF (acting on trkA receptors), extracellular ATP (acting on P2Y2 receptors), indirectly trigger and stimulate TRPV1 (Chuang et al. 2001; Ferreira et al. 2004; Hu et al. 2002; Moriyama et al. 2003; Premkumar 2010; Shin et al. 2002; Tominaga et al. 2001).

Thapsigargin

Thapsigargin is a sesquiterpine containing tricyclic diterpene ring, isolated from *Thapsia garganica* (Apiaceae). It acts as selective inhibitor of Ca^{2+}-ATPases (SERCAs) (Luo et al. 2000) in the endoplasmic and sarcoplasmic reticulum of animal cells. It is used traditionally in

Table 2 Structures and functions of TRP channel modulators

STRUCTURE	Agonist/Antagonist	Reference
 CAPSAICIN	TRPV1 Agonist	109
 CAMPHOR	TRPA1 and TRPV3 Agonist at low concentration TRPA1 Antagonist at high concentration	127
 CAPSAZEPINE	TRPV1 Antagonist	109
 YOHIMBINE	TRPV1 Antagonist	128
 2- Aminoethoxydiphenyl borate	TRPV1,TRPV2,TRPV3 Agonist at high concentration Non-selective TRP channel antagonist at low concentration	129
 THAPSIGARGIN	TRPV1 Agonist	130
 MECAMYLAMINE	TRPA1 Antagonist	131
 RESINIFERATOXIN	TRPV1 Agonist	132

treatment of rheumatic pain in European and Arabian medicine system and seems to be a prototype for TRPV1 inhibitor.

Yohimbine

An indole alkaloid, isolated from the root of *Rauwolfia serpentine* (Aponcynaceae) and bark of the tree *Pausinystalia yohimbe* (Rubiaceae), blocks Na^+ channels and TRPV1 receptors which revealed to hinder the firing activities of DRG neurons of rat (Dessaint et al. 2004).

Resiniferatoxin (RTX)

RTX is a naturally occurring ultrapotent analog of capsaicin found in resin spurge *Euphorbia resinifera* and *Euphorbia poissonii* having important anti-nociceptive properties (Walpole et al. 1996) mainly related to the dysfunction of various specific classes of pain receptors, but due to the stinging, burning pain and erythema primarily produced by these agonists make them difficult to use clinically.

2-aminoethoxydiphenylborate (2-APB)

2-APB is a synthetic diphenylborinic acid derivative that inhibits IP_3 receptors (Diver et al. 2001) and TRP channels. It activates TRPV1, TRPV2, and TRPV3 at higher concentrations (Bootman et al. 2002; Xu et al. 2005b). It manipulates intracellular Ca^{2+} release that modify TRP channel activity. Patients with pathological condition accompanied with persistent or recurrent severe pain, such as neuropathic, herpes zoster, arthritis, cancer, and postoperative pain, are treated with innervations that are inadequate and encompassing devastating side effects. Experimental evidences showed that the TRPV1 is involved in these different pathologies. TRPV1 ligands and modulators are emerging as a new pharmacotherapeutic approach for various painful conditions.

Non-pungent agonists of TRPV1 receptors may be an interesting alternative and are devoid of undesirable effect. Specific antagonists of TRP channels could be used clinically and expected to have more prompt effects, different from the affected sensory fiber destruction caused by agonists.

TRPM8 channels are involved in oxaliplatin, and chronic constriction nerve injury (CCI)-induced neuropathic pain and its antagonist have ability to treat cold-induced allodynia (Descoeur et al. 2011; Su et al. 2011; Xing et al. 2007). TRPM8 plays a role in core body temperature regulation and detection of TRPM8 antagonist (PF-05105679) shows its competence in treatment of pain in humans (Andrews et al. 2015).

Conclusions

TRPs are transmembrane ligand-gated Ca^{2+} channels that play pivotal role in cellular functioning. TRP channels mainly include TRPV1, TRPA1, and TRPM8 gates for Ca^{2+} ion exclusively and tend to increase the intracellular Ca^{2+} concentration. Increased Ca^{2+} may lead to numerous cellular consequences like muscular contraction, neurotransmitter release, release of Substance P, and action potential generation. Increasing intracellular Ca^{2+} activates other TRP channels and modulates cellular signalling that leads to generation and propagation of neuropathic pain. 5-HPETE, the metabolite of LOX pathway, and other arachidonic acid metabolites, and also activates the TRVP1 channels and precipitates neuropathic pain. Furthermore, modulation of TRP channels either by synthetic/natural agents or by inhibition of COX/LOX pathway relieves neuropathic pain.

TRP channels can be explored as potential therapeutic target for treatment of neuropathic pain. TRP channel modulators can be picked up Pharmaceutical Industries and developed as a new class of highly efficacious pharmacotherapeutic agents for the clinical management of neuropathic pain.

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