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REVIEW

TRPs and pain

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Abstract Nociception is the process of transmission of painful signals by nociceptors in the primary afferent nerve fibers, which specifically respond to noxious stimuli. These noxious stimuli are detected by nociceptors and converted into electrical signals, which are then transmitted to the spinal cord, thalamus, and the cerebral cortex, where pain is finally sensed. Transient receptor potential (TRP) ion channels have emerged as a family of evolutionarily conserved ligand-gated ion channels that function as molecular detectors of physical stimuli. Several member of this family, at least six channels from three TRP family subtypes (TRPV1–4, TRPM8, and TRPA1), are expressed in nociceptors, where they act as transducers for signals from thermal, chemical, and mechanical stimuli and play crucial roles in the generation and development of pathological pain perception. This review focuses on the increasing evidence of TRP channel involvement and contribution in nociceptive pain and the pain hypersensitivity associated with peripheral inflammation or neuropathy, and on the renewed interest in targeting TRP channels for pain relief.

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Pain is defined by the International Association for the Study of Pain (IASP) as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage." Painful signals generated by tissue damage are detected by nociceptors, which transfer the signals to the central nervous system to produce this unpleasant sensory and emotional experience. The two main types of nociceptors that detect painful signals are unmyelinated C-fibers and myelinated Aδ-fibers [1]. These nerve fibers use electrical signals, by means of action potentials, to convey noxious information rapidly to the brain. In the generation of these action potentials that carry the signal and produce the pain sensation, a crucial role is played by ion channels that are specifically expressed in the aforementioned nerve fibers. In recent years, ion channels such as transient receptor potential (TRP) channels, ATP channels, acid-sensing ion channels, and Piezo channels (whose opening causes the cation influx that depolarizes sensory neurons) have been identified as key pain receptors [2, 3]. Among these channels, certain TRP channels such as TRPV1–4, TRPA1, and TRPM8 have attracted considerable attention because they have been shown to be expressed in nociceptors, where they act as detectors and transducers for thermal, chemical, and mechanical stimuli. Activation or sensitization of these channels is deeply involved in the pathological pain condition. Pain can generally be classified as a nociceptive, inflammatory, or neuropathic condition depending on the pathogenesis. This review highlights the emerging role of TRP channels, with an emphasis on TRPV1 and TRPA1, in the peripheral mechanisms of these pain conditions.

TRPs in nociceptive pain as chemical and physical sensors

Nociceptive pain represents the normal response of somatic or visceral tissues to noxious insult or injury. This form of pain is typically the result of tissue damage caused by a noxious stimulus, but it is a critical component of the body's defense system that protects against further damage and heals the damaged tissue.

In the elucidation of the molecular mechanism of pain, limited progress was made until the capsaicin receptor (TRPV1) was cloned in 1997. TRPV1 was first reported by Caterina et al. as a nonselective cation channel that exhibits high calcium permeability [4]. TRPV1 is expressed by the peripheral and central terminals of small-diameter sensory neurons (nociceptors) in the dorsal root ganglion (DRG), trigeminal ganglion (TG), nodose ganglion (NG), geniculate ganglion (GG), and jugular ganglion [4–8], and TRPV1 modulates pain transmission at the first sensory synapse [9–12]. Approximately 35–50 % of all DRG or TG neurons were found to be TRPV1-positive [7, 13], and these represent a large population of unmyelinated C-fibers and a small population of thinly myelinated Ad-fibers. TRPV1 expression occurs largely in association with the expression of substance P and calcitonin gene-related peptide. TRPV1 functions as a polymodal receptor [14] because it is activated not only by capsaicin but also by noxious heat (≥43 °C), low pH (protons) [4, 6, 13], and several other exogenous or endogenous agents (Table 1) such as camphor [15], allicin [16, 17], spider toxins [18, 19], anandamide [20], arachidonic acid metabolites [21], *N*-arachidonoyl dopamine [22], oleoylethanolamide (OEA) [23], N-OEA [24], and polyamines [25]. Intra-cutaneous administration of these chemicals in animals induces pain-related behaviors, which suggests a role of TRPV1 in nociception.

TRPV1-deficient mice show a complete loss of physiological and behavioral responses to capsaicin, partial diminution in the responses to noxious heat, and normal responses to noxious mechanical stimuli [26, 27]. In sensory neurons from mice lacking TRPV1, in vitro calcium influx or electrophysiological response to capsaicin, protons, and heat is completely absent. TRPV1 is widely recognized as a heat sensor, but, intriguingly, TRPV1 null mice in certain studies showed normal sensitivity to acute noxious heat [28, 29], which suggests that other molecules might participate in the sensation of noxious heat when TRPV1 is not expressed.

TRPA1 is another nonselective cation channel of the TRP family that is critically involved in nociception. In the sensory nervous system, TRPA1 was reported to be expressed in the DRG [7, 30], TG [7], NG [31], superior cervical ganglion (SCG) [32], and GG [8, 33]. Interestingly, TRPA1 is highly coexpressed with TRPV1 in small-diameter nociceptors [7, 30, 34], which raises the question of functional specificity. Like TRPV1, TRPA1 also functions as a polymodal receptor: TRPA1 can be activated by multiple stimuli such as chemical, thermal (≤18 °C), mechanical, and osmotic stimuli [30, 35–37], as detailed next.

First, the TRPA1 channel functions as a chemical sensor and detects a remarkably broad range of chemicals (see Table 1), including exogenous chemicals such as the pungent ingredients of mustard oil, garlic, wintergreen oil, clove oil, ginger, and cinnamon oil, all of which induce acute painful burning or pricking sensation [16, 35, 38, 39]; and endogenous chemicals that are produced during oxidative or nitrative stress, including α,β-unsaturated aldehydes such as 4-hydroxynonenal (4-HNE), cyclopentenone, prostaglandin metabolites such as 15d-PGJ_2, hydrogen peroxide/hydroxyl radicals, and nitrooleic acid [40–44]. Most of these chemicals are electrophilic and have been shown to activate TRPA1 by covalently modifying cysteine residues in the channel [45, 46]. The nociception caused by these reactive chemicals is drastically reduced or eliminated in TRPA1 knockout mice [45, 47, 48]. Conversely, TRPA1 can also be activated by certain nonelectrophilic chemicals such as thymol [49], NSAIDs such as flufenamic acid and niflumic acid [50], isoflurane [51], farnesyl thiosalicylic acid [49, 52], 1,4-dihydropyridines [53], nicotine [54], and icilin [30]. The sensory qualities of most of these chemicals are clearly related to their noxious stimuli, and this supports the view that TRPA1 is a key sensor of chemical damage.

Second, TRPA1 has been suggested to serve as a thermal sensor of noxious cold stimuli [30, 38, 55], although cold-induced TRPA1 activation is substantially weaker than the activation induced by allyl isothiocyanate [56]. This finding was supported by two independent studies in which TRPA1 knockout mice displayed impaired response to cold [56, 57]. However, this property remains controversial because other studies failed to confirm direct, cold-induced TRPA1 activation, and TRPA1-deficient mice were also found to show normal cold sensitivity [31, 35, 58].

Third, TRPA1 might also detect mechanical nociceptive stimuli, although this idea requires further verification. Among TRPs, the TRPA1 channel possesses a unique structure composed of several ankyrin repeats in the N terminus; these repeats have been hypothesized to act as a spring when under mechanical stress [59]. In *Drosophila* and *Caenorhabditis elegans*, TRPA1 has been demonstrated to be involved in mechanical nociception [60, 61]. In mammals, TRPA1 expressed in mechanosensitive hair cells of the inner ear has been proposed to function as a putative mechanosensor [31, 37]. Furthermore, mice deficient in TRPA1 display impaired behavioral sensitivity to punctate mechanical stimuli [57]. In one study in which skin-nerve preparations from TRPA1-deficient mice were used, cutaneous fibers were demonstrated to exhibit a drastic reduction in their firing rate in response to mechanical stimuli [62]. In another study, under acute pharmacological inhibition of TRPA1 achieved through antagonist application to the receptive field, cutaneous fibers were shown to exhibit

Table 1 TRPs and modulators

TRPs	Exogenous agonists	Endogenous agonists; activators	Antagonists; inhibitors	Intracellular modulators
TRPV1	2-APB	2-AG	5′-I-RTX	Calmodulin
	Allicin	12-(s)-HPETE	A 784168	CaMKII
	Camphor	15-(s)-HPETE	Adenosine	Diacylglycerol
	Cannabidiol	5-(s)-HETE	BCTC	Intracellular calcium
	Cannabigerol	Ammonia	Capsazepine	P38
	Capsaicin	Anandamide	Cholesterol	PI3K
	Etodolac	Extracellular calcium	PME	PIP2
	Eugenol	Extracellular Mg^{2+}	Resolvin D2 and E1	PKA
	Evodiamine	Extracellular protons	Ruthenium red	PKC
	Gingerol	Leukotriene B4	Thapsigargin	PLA
	Hydrogen sulfide (H_2S)	LPA	Yohimbine	PLC
	Olvanil	NADA		
	Piperine	Nitric oxide		
	Polygodial	*N*-Oleoylethanolamide		
	Resiniferatoxin	Oleoylethanolamide		
	Spider toxins	Palmitoylethanolamide Polyamines		
		PUFAs		
		Temperature (≥43 °C)		
TRPA1	1,4-Dihydropyridines	4-Hydroxynonenal	A 967079	CMCR
	2-APB	4-Oxononenal	AP 18	Diacylglycerol
	Acrolein	5′ 6′-EET	AZ465	Intracellular alkalization
	Allicin	Bradykinin	Borneol	Intracellular calcium
	Allyl isothiocyanate	Cyclopentenone prostaglandins	Camphor	PIP2
	Apomorphine	H_2O_2	Chembridge-5861528	PKA
	Auranofin	Methylglyoxal	HC-030031	PLC
	Cannabichromene	Nicotine	Resolvin D1 and D2	
	Cannabidiol	Nitric oxide	Resveratrol	
	Cannabinol	Nitrooleic acid	Ruthenium red	
	Capsiate	Polysulfide	Thymol	
	Cinnamaldehyde	Temperature (≤17 °C)		
	Curcumin	Tetrahydrocannabinol		
	Diphenyleneiodonium			
	Eugenol			
	FTA			
	Flufenamic acid			
	Formalin			
	Garlic			
	Gingerol			
	Hydrogen sulfide			
	Icilin			
	Isoflurane			
	Niflumic acid			
	Streptozotocin			
	Tetrahydrocannabinol			
TRPV2	2-APB	IGF-I	Lanthanum	CaMKII
	Cannabidiol	Lysophosphatidylcholine	Ruthenium red	PKA
	Carvacrol	Lysophosphatidylinositol	SKF96365	
	Probenecid	Temperature (≥52 °C)	Tranilast	
TRPV3	2-APB	Arachidonic acid	GRC15300	Calmodulin
	6-*Tert*-butyl-m-cresol	Farnesyl pyrophosphate	Icilin	Intracellular calcium
	Borneol	Temperature (≥34 °C)	Isopentenyl pyrophosphate	
	Camphor		Resolvin D1	
	Carvacrol			
	Carveol			
	Eugenol			
	Incensole acetate			
	Dihydrocarveol			
	Menthol			
	Thymol			
TRPV4	4-alpha PDD	5′ 6′-EET	Gadolinium	Calmodulin
	Apigenin	8′ 9′-EET	GSK 2193874	cAMP
	Bisandrographolide A	Anandamide	HC 067047	Intracellular calcium

Table 1 (continued)

TRPs	Exogenous agonists	Endogenous agonists; activators	Antagonists; inhibitors	Intracellular modulators
	Citrate	Citric acid	Lanthanum	PKA
	GSK 1016790	Cytochrome P450	Resolvin D1	PKC
	Phorbol esters	DMAPP	RN 1734	PLA2
	RN 1747	Eicosanoid	Ruthenium red	Src tyrosine kinase
		Low PH		
		N-Acyl taurine		
		Nitric oxide		
		Temperature (≥27 °C)		
TRPM8	Eucalyptol	3-Iodothyronamine	5-Benzyloxytryptamine	Calmodulin
	Geraniol	Lysophospholipids	AMTB	Intracellular calcium
	Hydroxycitronellal	Temperature (≤25 °C)	Arylglycine derivatives	PIP2
	Icilin		BCTC	PKA
	Linalool		Benzimidazoles	PKC
	MC		Capsazepine	PLA2
	Menthol		M8-An	
	NCD		PUFAs	
			Tetrahydroisoquinoline	

Abbreviations: *2-AG* arachidonoyl glycerol, *2-APB* 2-aminoethoxydiphenylborane, *4-alpha PDD* 4 alpha phorbol 12,13-didecanoate, *AMTB N*-(3-aminopropyl)-2-{[(3-methylphenyl)methyl]oxy}-*N*-(2-thienylmethyl) benzamide hydrochloride salt, *BCTC N*-(4-*tert*-butylphenyl)-4-(3-chloropyridin-2-yl) piperazine-1-carboxamide, *cAMP* cyclic adenosine 3′,5′-monophosphate, *CMCR* covalent modification of cysteine residues, *DMAPP* dimethylallyl pyrophosphate, *EET* epoxy eicosatrienoic acids, *FTA* farnesyl thiosalicylic acid, *HETE* hydroxy eicosatetraenoic acid, *HPETE* hydroperoxy eicosatetraenoic acid, *IGF-I* insulin-like growth factor-I, *I-RTX* 5-iodoresiniferatoxin, *LPA* lysophosphatidic acid, *MC* menthane carboxamide; *NAEs N*-acyl ethanolamines, *NADA N*-arachidonoyl dopamine, *NCD* neomenthane carboxamide derivatives, *PI3K* phosphoinositide 3-kinase, *PIP2* phosphatidylinositol 4,5-bisphosphate, *PKA* protein kinase A, *PKC* protein kinase C, *PLA* phospholipase A, *PLC* phospholipase C, *PME* pinosylvin methyl ether, *PUFA* polyunsaturated fatty acid

markedly decreased firing rates in response to mechanical stimuli [63]. Moreover, Brierley et al. used in vitro electrophysiological and pharmacological approaches and observed that TRPA1 is required for normal mechanosensory function in specific subsets of vagal, splanchnic, and pelvic afferents, and further found that behavioral responses to noxious colonic distension were substantially reduced in TRPA1-deficient mice [64]. A recent study also indicated that TRPA1 mediates mechanical currents in the plasma membrane; in this study, direct recordings of cultured mouse sensory neurons were obtained under application of a rapid, focal mechanical stimulation to the soma membrane [65]. Collectively, this emerging evidence suggests that TRPA1 plays a role in mechanosensitivity.

Other TRP channels such as TRPV2, V3, V4, and M8 have been suggested to contribute to pathological pain in various disease states. However, the role of these channels in detecting nociceptive pain is poorly understood. Their agonists and antagonists are listed in Table 1. TRPV2 is activated by high temperature (≥52 °C) [66], which is consistent with the temperature range sensed by Ad-fibers [67, 68]. Based on this activation feature and on the expression of TRPV2 mainly in medium-sized primary afferents that do not express TRPV1, TRPV2 has been suggested to act as a high-threshold temperature sensor in Ad nociceptors [66, 69, 70]. However, evidence from studies conducted using knockout mice does not support an acute heat-sensing role for TRPV2 [29, 71].

TRPV3 is activated by warm temperature (≥34 °C) [72–74] and certain chemical agents, including camphor, menthol, carvacrol, eugenol, insensol, and 2-aminoethoxydiphenyl borate [75–81]. A role of TRPV3 in thermosensation was revealed in knockout mice, which showed strong deficits in response to innocuous and noxious heat but not in other sensory modalities [76]. TRPV3 is prominently expressed in—and functions in—skin keratinocytes, although both peripheral and central neurons, including neurons in the DRG, TG, SCG, spinal cord, and certain brain regions, are also TRPV3-positive [72–74]. In keratinocytes, TRPV3-mediated currents and calcium influx have been reported [82, 83], but evidence supporting functional TRPV3 expression in sensory neurons has not been obtained. The TRPV3 expressed in skin keratinocytes might participate in sensing physical stimuli by means of signal relay to sensory nerve endings through chemical mediators such as ATP and prostaglandin E2 [72, 84–87].

TRPV4 is another thermosensor that is activated by warm temperature (≥27 °C) [88, 89]. Unlike other thermo-TRP channels, TRPV4 was originally detected as an osmosensory channel that is activated by extracellular osmolarity (hypotonic cell swelling) and was expected to function as a putative mammalian mechanosensitive channel [90–92]. Furthermore, TRPV4 is not only activated by physical stimuli but also various stimuli ranging from exogenous to endogenous chemicals such as anandamide and arachidonic acid [93], bisandrographolide [94], 4-alpha-phorbol 12,13-didecanoate [95], acetylcholine [96], apigenin [97], and dimethylallyl pyrophosphate [98].

Therefore, like TRPV1 and AI, TRPV4 can be also defined as a polymodal receptor. Moreover, TRPV4 is expressed by a wide range of tissues, including in the sensory neurons present in the DRG, TG, and NG [99–101]. Mice lacking TRPV4 display a marked reduction in sensitivity to pressure, which suggests an essential role of TRPV4 in the normal detection of pressure and as a receptor of the high-threshold mechanosensory complex [102].

TRPM8 is defined as a sensor of cool temperatures (≤25 °C) [103, 104], and it can also be activated by cooling compounds such as menthol, icilin, and several other agents [38, 103–106]. TRPM8 is expressed in a small population of nociceptors located in the DRG and TG that do not express TRPV1 [7, 103, 104]. Given that most nociceptors are TRPV1-positive neurons, the lack of TRPM8 coexpression with TRPV1 suggests that TRPM8 is not involved in the detection of noxious stimuli. Nevertheless, a recent study involving selective cell ablation demonstrated that TRPM8-containing neurons are required for noxious cold aversion [107].

Taken together, TRP channels in peripheral sensory neurons (or in keratinocytes) act as sensors of various stimuli. Such stimuli from outside of the body (exogenous agonists) stimulate directly certain TRP channels and evoke nociceptive pain (Fig. 1). Meanwhile, endogenous agonists are often induced or upregulated following pathological conditions such as inflammation or nerve injury, which in turn stimulate their receptors (TRP channels) and contribute to the inflammatory or neuropathic pain as one potential mechanism.

TRPs in inflammatory pain

Inflammatory pain results from the activation and sensitization of the nociceptive pain pathway—characterized by a reduced threshold and an increased responsiveness of sensory neurons—by a variety of mediators released at the sites of tissue inflammation. These mediators, which include proinflammatory cytokines, chemokines, reactive oxygen species, protein kinases, vasoactive amines, lipids, ATP, acids, and other factors, might be released by infiltrating leukocytes, vascular endothelial cells, or tissue-resident mast cells after tissue injury. The mediators associated with the inflammatory response directly or indirectly stimulate or sensitize peripheral sensory neurons (nociceptors), which results in a reduction in the activation threshold of the nociceptors and an increase in their responsiveness. The activation or sensitization (or both) of TRP channels in the sensory nerve during inflammation is considered to be the major mechanism underlying inflammatory pain (Fig. 2a).

Studies conducted using knockout mice have clearly demonstrated the essential roles of certain TRP channels in the initiation or maintenance of inflammatory pain. In TRPV1-deficient mice, the development of inflammatory thermal hyperalgesia was defective but mechanical hypersensitivity was unchanged [26–28, 108, 109], whereas TRPA1-deficient mice exhibited markedly reduced development of hyperalgesia in response to injections of inflammation-related chemicals, including formalin, 4-HNE, prostaglandin metabolites, H_2O_2, and bradykinin [41, 45, 47, 48, 58, 110]. TRPV4 is another TRP family member that might contribute

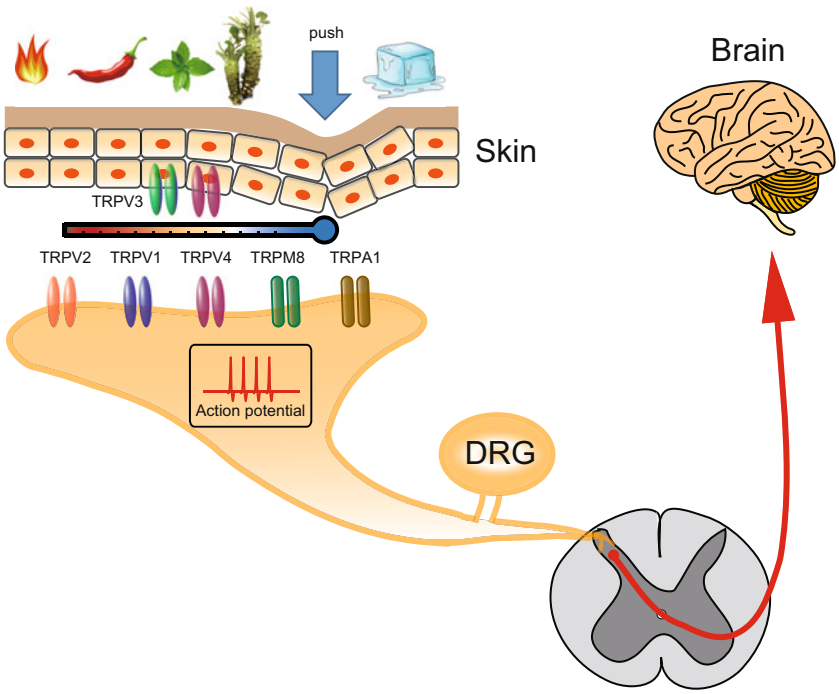

Fig. 1 TRPs in nociceptive pain

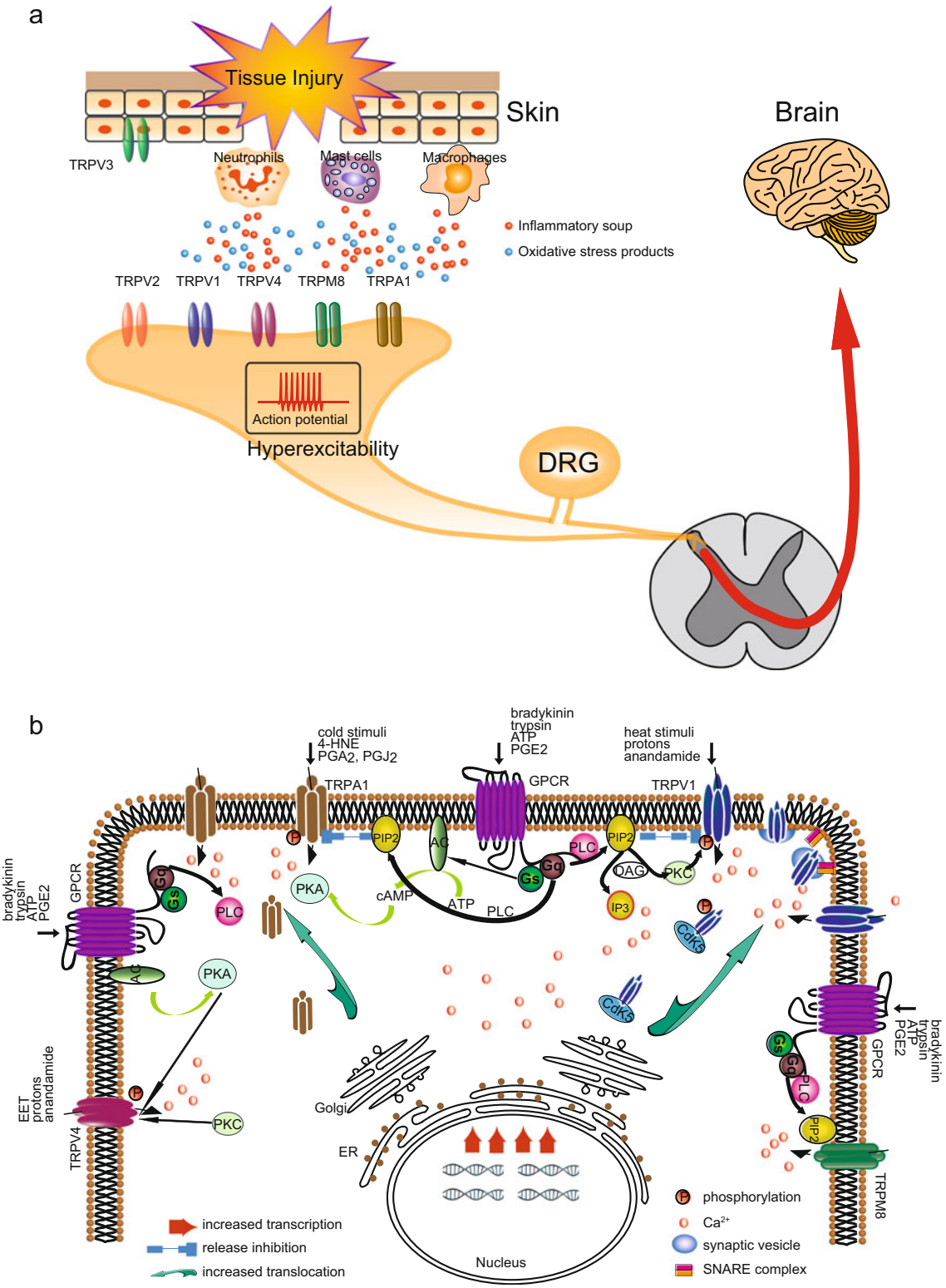

Fig. 2 TRPs in inflammatory pain. **a** Inflammatory soup and oxidative products activate and/or sensitize TRPs in peripheral sensory neurons. **b** Intracellular mechanisms involved in TRP channels' sensitization

to inflammatory pain; results obtained using TRPV4-deficient mice indicate that this channel is required for the development of thermal hyperalgesia induced by both cutaneous and colonic inflammation [111–115]. Conversely, TRPV2 might not be involved in inflammatory pain: as compared with wild-type mice, TRPV2 knockout mice showed no change in

thermal and mechanical responses in a model of inflammation (induced by complete Freund's adjuvant (CFA)) [71]. TRPV3 expressed in skin keratinocytes might play a role under inflammatory conditions by enhancing the peripheral input through inflammatory mediators [84, 85, 116]. TRPM8 was demonstrated to contribute the cold-induced hyperalgesia observed in inflammation produced by CFA; this hyperalgesia was impaired in TRPM8 knockout mice [117].

TRPs might participate in inflammatory pain through two mechanisms. In one mechanism, certain products released from inflamed tissues, including arachidonic acid derivatives such as anandamide, 15d-PGJ2, and 12-(S)-HPETE, and oxidative stress products such as 4-HNE and H_2O_2, might function as endogenous TRPV1, V4, or A1 activators and directly stimulate them and contribute to spontaneous pain [41, 48, 93, 110, 118–120]. These findings demonstrate that TRPs could contribute to inflammatory pain by acting as the terminal substrate for inflammatory mediators. Sensitization of TRPs is considered to be another potential mechanism underlying inflammatory pain. In the development of inflammatory pain, three cellular and molecular mechanisms have been established (Fig. 2b). First, inflammation might increase TRP channel expression in sensory neurons either transcriptionally or posttranslationally. For example, peripheral inflammation increases TRPV1 levels in nociceptor peripheral terminals in a transcription-independent manner and contributes to the maintenance of inflammatory heat hypersensitivity [121]. By contract, peripheral inflammation induces transcriptional upregulation of TRPA1 (but not TRPM8) in DRG neurons and thus contributes to inflammatory cold hyperalgesia [122]. Moreover, neurotrophic factors, including members of the nerve growth factor and glial cell-derived neurotrophic factor families, have been suggested to be involved in the gene regulation of both TRPV1 and TRPA1 [121–126]. Second, because TRP channels are transmembrane receptors, the number of functional TRP channels present in the plasma membrane is a critical determinant of channel function. Emerging evidence has demonstrated that inflammatory mediators induce a rapid translocation of TRP channels from the cytoplasm to the plasma membrane following the activation of second-messenger pathways and subsequent posttranslational modification such as channel phosphorylation or glycosylation [127–134]. Numerous proinflammatory agents and trophic factors have been suggested to sensitize TRP channels through posttranslational regulation; these molecules include CCL3 [135], bradykinin [136–138], serotonin [139], histamine [140], glutamate [10, 127, 141], PGE2 [142], ATP [143], trypsin/tryptase [144, 145], NGF [131], and insulin/insulin-like growth factor 1 [128, 146, 147]. Phosphorylation is one of the molecular mechanisms involved in the sensitization of TRP channels. Inflammatory mediators act on receptors that are coupled to either G proteins or tyrosine kinase pathways and thus activate phospholipase C (PLC) and/or adenylate cyclase; this, in turn, induces second-messenger pathways such as those involving protein kinase C (PKC), protein kinase A (PKA), and/or phosphoinositide 3-kinase (PI3K) activation and leads to channel phosphorylation. Previous studies have shown that PKC activation-sensitized, SNARE-dependent exocytosis, and Src-PI3K-dependent phosphorylation of TRPV1 are involved in the channel's membrane insertion under inflammatory conditions [127, 129, 148] and that cyclin-dependent kinase 5 might regulate the transport of TRPV1 from the Golgi apparatus to the plasma membrane [149]. Third, in addition to the translocation of the channels from the cytoplasm to the membrane, channel phosphorylation and a disinhibition mechanism might alter the channel structure and functionally enhance channel sensitivity. Inflammatory mediators might sensitize TRPs by releasing the inhibition of TRP channels, which is subjected to regulation by phosphatidylinositol 4,5-bisphosphate turnover mediated by PLC activation [34, 150, 151].

TRPs in neuropathic pain

Neuropathic pain is initiated or caused by a primary lesion or disease in the somatosensory nervous system; this type of pain includes the pain in diabetic neuropathy or chemotherapy-related peripheral neuropathy, postherpetic neuralgia, spinal cord injury pain, and phantom limb pain. Pathophysiological changes in primary sensory neurons induced by nerve injury and disease and the consequent changes in signal processing in the central nervous system constitute the underlying mechanism of neuropathic pain. Following peripheral nerve damage, TRP channel expression changes dynamically in sensory neurons. First, the expression of TRP channels, including TRPV1, TRPA1, TRPV3, and TRPM8, decreases in the injured neuron in response to peripheral axonal damage; this downregulation of TRP channels might be a result of the loss of trophic support following injury [8, 13, 122, 152–154]. Concurrently, however, certain TRP channels, such as TRPV1 and TRPA1, are upregulated in nearby spared neurons following nerve injury, and this increase correlates closely with behavioral change [13, 122, 152–154]. In studies conducted using human tissue, TRPV1 and TRPV3 levels were found to be decreased in the skin of patients with diabetic or other painful neuropathies but increased in intact nerve fibers in certain patients with pain hypersensitivity, whereas the level of TRPV4 was observed to remain unchanged [99, 155]. One potential mechanism has been suggested for these phenotypic changes: the damaged neurons might release growth factors and neurotransmitters into the surrounding area and, consequently, cause an increase in the excitability of surrounding neurons [13, 153, 156, 157]. These dynamic changes contrast the changes detected in inflammation, in which TRP channels are generally upregulated (see above); this reflects the notion

that inflammatory pain simply features a "surplus" of nociceptive signaling, whereas the sensory abnormalities of neuropathies include not only hypersensitivity (hyperalgesia or allodynia), but also paresthesias, hypoesthesia, or complete deficits perceived as numbness [158] (Fig. 3).

In addition to the drastic phenotypic change observed as alterations in TRPV1 and A1 channel expression patterns, knockdown or pharmacological inhibition of these TRPs has been widely demonstrated to reduce pain behavior in several animal models of neuropathic pain [122, 154, 159–178]. Interestingly, however, studies conducted using knockout mice have provided little evidence supporting the notion that these TRPs (TRPV1 and TRPA1) are essential contributors to the development of neuropathic pain. For example, knockout of TRPV1 or TRPA1 typically exerts no effect on pain behaviors induced by nerve injury [26, 27, 57] or diabetes [179]. By contrast, mechanical hyperalgesia induced by paclitaxel, vincristine, or diabetes was strongly reduced in TRPV4 knockout mice, and knockdown or pharmacological inhibition of TRPV4 reduced chemotherapy-induced mechanical or hypotonic hyperalgesia [173, 180]; this suggests a critical role of TRPV4 in mechanotransduction in the setting of nerve injury [181]. Conversely, TRPM8 null mice display a marked reduction in injury-induced responsiveness to acetone cooling [117], and pharmacological blockade of TRPM8 leads to a reduction in nerve injury-induced cold hypersensitivity [182], which indicates that TRPM8 might play a role in cooling-induced neuropathic pain. Furthermore, recent studies have suggested the involvement of TRPM2 in nerve injury-induced mechanical allodynia [183–185].

In conclusion, TRPs act as chemical, thermal, and mechanical sensors in nociceptors and detect nociceptive pain. Certain TRPs—particularly TRPV1 and TRPA1—are essential for the development of hyperalgesia and allodynia under inflammatory conditions, whereas TRPV4 and TRPM8 might contribute to neuropathic hypersensitivity to mechanical and cold stimuli, respectively. However, the essential role of all such TRP channels in the development of neuropathic pain remains to be further identified, although antagonists of certain TRPs have been shown to reduce the pain behavior following nerve injury.

TRPs as targets of analgesics

The roles of TRP channels in mediating pathological pain make them potential targets for analgesics. TRP channels are located in nociceptors where pain is generated, and thus the simplest access for analgesics would involve blocking the channels directly. Two main approaches have been proposed to inhibit TRP channels: blocking the channel activity using antagonists and, paradoxically, stimulating the channels to desensitize them. Drug development studies have focused on TRPV1, TRPV3, TRPM8, and TRPA1, which have been clearly demonstrated to be involved in pathological pain (see above). Currently, at least seven antagonists of TRPV1, two of TRPA1, and one of TRPV3 are being clinically tested by pharmaceutical industries [186–188]. However, as discussed in the preceding section, several TRP channels perform dual functions: they act as sensors/detectors of nociceptive signals under normal conditions, which helps prevent tissue damage, and they also act as contributors to inflammatory or neuropathic pain under pathological conditions, and this can pose a risk of noxious perception being blunted when the channels' activity is blocked. In accord, in healthy human volunteers, increase in heat pain threshold was observed after the

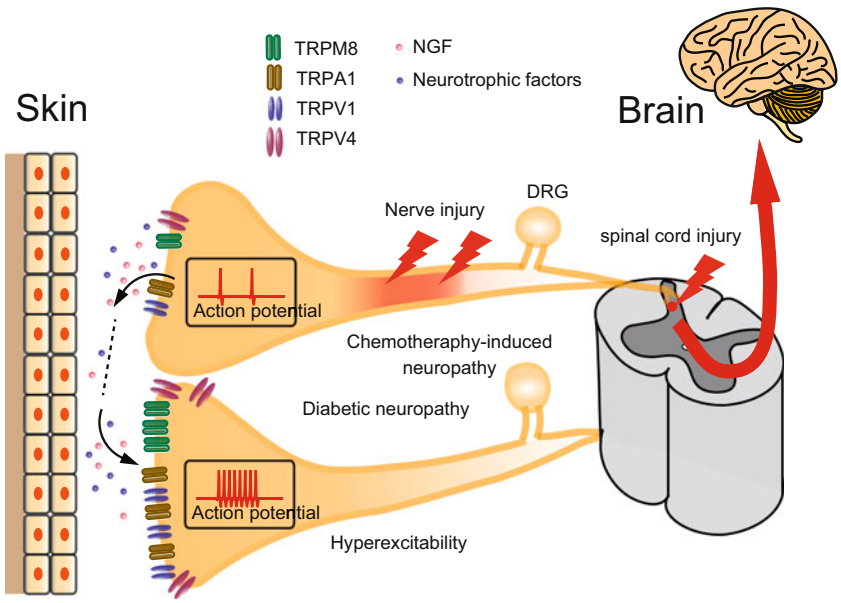

Fig. 3 TRPs in neuropathic pain

administration of TRPV1 antagonists, including SB-705498 [189], MK-2295 [190], ABT-102 [191], and AZD1386 [192]. Hyperthermia is another adverse effect of TRPV1 antagonists; almost all TRPV1 antagonists undergoing clinical development, such as AMG517 (Amgen) [193], ABT-102 (Abbott) [191], and AZD1386 (AstraZeneca) [192], caused hyperthermia in human volunteers that in certain cases lasted for 1–4 days, with core body temperatures rising up to 40.2 °C [193].

In contrast to the challenges associated with developing antagonists, in the case of agonists that have been applied to locally desensitize TRP channels and have been used clinically, severe adverse effects have not been reported, although the agonists might produce initial irritation or even degeneration of sensory nerves. This notion of a paradoxical use of agonists might be derived from the experience gained with certain herbal remedies used in traditional medicine. For example, preparations or prescriptions containing agonists of TRP channels, such as menthol (TRPM8), cinnamaldehyde (TRPA1), or shogaol (TRPV1), have long been used topically or orally to relieve neuralgia, arthralgia, menstrual pain, and headache in traditional Chinese medicine. Moreover, capsaicin-containing creams, occlusive patches, and liquid formulations have been developed and used for treating chronic painful conditions such as diabetic neuropathy, postherpetic neuralgia, and other painful disorders [186, 194–196]. A recent study analyzed several related human studies involving a total of over 2000 participants, and the results indicated that high-concentration capsaicin patches were effective in the treatment of postherpetic neuralgia and HIV neuropathy [197]. As an ultrapotent analog of capsaicin, resiniferatoxin has been developed preclinically for treating intractable cancer pain through intrathecal administration [186, 198]. Furthermore, clinical trials have shown beneficial effects of topically administered peppermint oil in alleviating thermally elicited pain and postherpetic neuralgia [199, 200]; in accord, the results of animal experiments have shown that oral menthol administration can cause short-term analgesia [201]. Icilin and menthol might also reduce mechanical and thermal hypersensitivity caused by peripheral nerve injury [202]. The minor side effects observed with these agonists provide useful information for developing TRP-targeted analgesics.

As discussed in preceding sections, the sensitization of TRPs contributes to inflammatory and neuropathic pain. In addition to simply blocking TRP channels by using antagonists, an alternative strategy for developing analgesics that target TRPs involves preventing or reducing TRP sensitization. Targeting the channels by using endogenous modulators is an attractive approach for controlling TRP activity. As already noted, numerous intracellular and extracellular agents might activate/sensitize or inhibit TRP channels, and thus interfering with these processes might result in analgesia. For example, inhibition of PKCε has been reported to completely block both inflammatory mediator-induced TRPV1 sensitization and heat hyperalgesia [203, 204]. Another study recently reported that disrupting the interaction between TRPV1 and A-kinase-anchoring protein 79/150 using inhibitory peptides prevents TRPV1 sensitization and inflammatory hyperalgesia [205]. Furthermore, endogenous inhibitors of TRPV1/A1, such as resolvins [206] and artemin [207], have been proposed for use in the treatment of pain conditions. These attempts might yield novel ideas for maximizing the reduction of the activity of sensitized TRPs while concurrently minimizing any disruption of their sensor functions.

Conclusions

Eighteen years have passed since the first pain sensor, TRPV1, was cloned [4]. During this period, numerous pain-related TRP channels have been discovered and comprehensively investigated. The rapid progress in the identification and characterization of TRP channels has enhanced our understanding of both nociceptive and pathological pain. Based on the growing knowledge of the TRP channels and their involvement in distinct pain conditions, we can expect pharmacological interventions targeting TRPV1/A1 channels to be effective in the treatment of chronic inflammatory syndromes that involve thermal hyperalgesia; conversely, targeting TRPV4 or TRPM8 should be effective for treating neuropathic conditions that include mechanical or cold hypersensitivity, respectively, in diseases that involve nerve injury or neuropathy. Moreover, several TRPs are expressed in a board range of tissue and organs that are outside the somatosensory system; thus, in addition to functioning as pain sensors or enhancers, these channels might perform other functions in organisms and might be involved in various diseases. Consequently, pharmacological inhibition of TRP channels might produce both clinical benefits for analgesia and unexpected adverse effects, such as the hyperthermia noted in the preceding section. To overcome these challenges, further investigation must be conducted using newly devised approaches, such as the discovery of second-generation antagonists or selective delivery of drugs through topical application or local injection instead of systemic administration.

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Conflict of interest The author declares that he has no conflict of interest

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