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Review

The role of the vanilloid (capsaicin) receptor (TRPV1) in physiology and pathology

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Abstract

The cloning of the vanilloid receptor 1 opened a floodgate for discoveries regarding the function of this complex molecule. It has been found that, in addition to heat, protons and vanilloids, this receptor also responds to various endogenous ligands. Furthermore, it has been also emerged that, through associations with other molecules, the vanilloid receptor 1 plays an important role in the integration of various stimuli and modulation of cellular excitability. Although, originally, the vanilloid receptor 1 was associated with nociceptive primary afferent fibres, it has been gradually revealed that it is broadly expressed in the brain, epidermis and visceral cells. The expression pattern of the vanilloid receptor 1 indicates that it could be involved in various physiological functions and in the pathomechanisms of diverse diseases. Here, we summarise the molecular, pharmacological and physiological characteristics, and putative functions, of the vanilloid receptor 1, and discuss the therapeutic potential of this molecule.

Keywords: Capsaicin; Primary sensory neuron; Brain; Viscera; Pain; Inflammation

Contents

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1. Introduction

From the physiological point of view, capsaicin, the active agent found in hot chilli peppers is perhaps one of the most enigmatic deterrent molecules ever produced by plants. Capsaicin accomplishes its effect by evoking sharp burning pain sensation when it comes in contact with mucous membranes. However, only mammals are affected.

It has been speculated that capsaicin-production gives a biological advantage to hot chilli peppers over non-hot ones, as mammals, which reduce the germinating capability of seeds are discouraged from eating the hot fruit, while other animals, such as birds, which pass the seeds without affecting their germinating ability can eat them freely. Thus, seed disposal is more effective for hot than for non-hot peppers (Tewksbury and Nabhan, 2001). Nevertheless, the deterrent effect of capsaicin seems to be less effective in humans than in other mammals. Despite the burning pain we experience (often twice) by eating hot dishes, the majority of us still find eating hot chilli pepper-containing meals highly enjoyable. Although it is undoubtedly an intriguing dilemma why most people enjoy the capsaicin-induced burning pain sensation, scientists for more than a century have rather been puzzled over other biological effects of capsaicin.

It has been well known that following the burning pain sensation, a long-lasting unresponsiveness of the capsaicin-exposed mucous membrane or skin to noxious stimuli develops; an effect that has been used by native Americans for controlling pain. In addition to the pain-related effects, physiologists in the 19th and 20th century found other profound effects including hyperactivity of various viscera followed by reduced reflex activity of the same organs, hypotension followed by hypertension, bradycardia followed by tachycardia, bronchoconstriction, coughing, hypothermia and extravasation (Donnerer and Lembeck, 1983; Fuller et al., 1985; Gamse et al., 1980; Green et al., 1984; Jancsó-Gábor et al., 1970; Jancsó and Such, 1983; Maggi et al., 1984) produced by topical or systemic capsaicin applications. The obscurity over the capsaicin-evoked biological effects started to clear up in the second half of the 20th century, mainly by the work of Hungarian scientists. Pórszász and Jancsó (1959) were the first to show that capsaicin selectively and specifically excites a subpopulation of primary sensory fibres, which can also be activated by noxious stimuli, and that capsaicin-sensitivity of the fibres is quickly reduced following capsaicin exposure. Jancsó-Gábor et al. (1970) found that, in addition to a subpopulation of primary sensory neurons, capsaicin also activated and induced damage, in a group of hypothalamic neurons, which are responsible for thermoregulation. Later, Jancsó et al.'s (1977) finding that capsaicin injection into neonatal rats results in the loss of capsaicin-sensitive primary sensory neurons provided an excellent tool for studying this subpopulation of sensory neurons. Studies on animals injected with capsaicin neonatally indicated that capsaicin evokes its effects through a specific receptor, and that the capsaicin receptor might be involved in the development of various pathological events, such as that of pain, visceral hyper-reflexia and neurogenic inflammation (Jancsó et al., 1977; Maggi et al., 1989; White and Helme, 1985). Szallasi et al.'s binding studies (Szallasi and Blumberg, 1990) in the early 1990s provided unquestionable evidence for the existence of a capsaicin-responsive receptor. As the capsaicin-sensitive receptor also responds to other related molecules with vanilloid moiety, the putative capsaicin receptor was named the "vanilloid receptor" (Szallasi and Blumberg, 1990).

The possibility that the vanilloid receptor could provide effective control over various pathological events prompted many laboratories to find the mechanisms through which the vanilloid receptor operates. This work got an extra momentum from the recent identification and characterisation of the receptor, named vanilloid receptor 1 (VR1 or TRPV1) (Caterina et al., 1997; Nagy and Rang, 1999; Tominaga et al., 1998), and the development of TRPV1 knock-out mice (Caterina et al., 2000; Davis et al., 2000). Results of these studies have provided evidence that

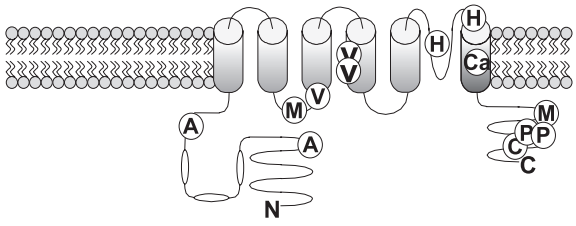

Fig. 1. Putative membrane configuration of TRPV1 with the approximate location of residues involved in ligand-binding and post-translational modifications. TRPV1 has six putative transmembrane domains, with both the N- and C-termini located intracellularly. The fifth and sixth transmembrane domains are connected by an intramembranous loop, which is involved in the formation of the pore. The structure of TRPV1 is similar to that of other members of the TRP family. V: residues involved in vanilloid binding, H: residues involved in proton binding, A: residues which are targets for PKA, C: residues which are targets for PKC, M: residues which are targets for CaMkII, P: residues involved in PtdIns(4,5)P_2 binding, Ca: residue involved in regulating Ca^{2+} permeability. Modified from figure 1B and C, figure 2B and C and figure 8 of Nagy and Rang: J. Neurosci. 19:10647-10655. Copyright 2004 by the Society for Nueroscience.

TRPV1 is indispensable for the development of certain pathological conditions, such as inflammatory heat hyperalgesia or visceral hyper-reflexia (Caterina et al., 2000; Davis et al., 2000; Avelino et al., 2003). However, the list of diseases in which TRPV1 might be involved is increasing. Recent studies shed light on the mechanisms through which TRPV1 is activated in pathological conditions. In the present review, we give an update on findings concerning the role of TRPV1 in the development of various diseases.

2. Molecular biology, physiology and pharmacology of the capsaicin receptor

The cloned TRPV1is a ~95-kDa protein (Caterina et al., 1997). Both the N- and C-termini are intracellular and the N-terminus has three ankarin repeat domains. So far, only one splice variant of TRPV1, the VR.5′ sv has been found (Schumacher et al., 2000). In addition, human TRPV1 shows polymorphism (Hayes et al., 2000).

The predicted structure of TRPV1 shows that it has six transmembrane domains with an additional intramembrane loop connecting the fifth and sixth transmembrane domains (Caterina et al., 1997) (Fig. 1). The structure and amino acid sequence of TRPV1 is similar to those of the transient receptor potential (TRP) family of cation channels (Caterina et al., 1997; Corey, 2003). The TRP family has at least six subfamilies in various species, TRPA, TRPC, TRPM, TRPN, TRPP and TRPV, with the vanilloid receptor 1 belonging to the latter one (Corey, 2004).

TRPV1, as other TRP proteins, has several consensus phosphorylation sequences: seven for protein kinase A (PKA) (Mohapatra and Nau, 2003), six for protein kinase C (PKC) (Bhave et al., 2003) and six for Ca^{2+}/calmodulin-dependent kinase II (CaMkII), (Jung et al., 2004). Some of the motifs are targets for more then one protein kinase (Fig. 1). TRPV1 also has several glycosylation sites, domains which link it to other proteins, and two Walker-type nucleotide-binding sites (Kwak et al., 2000). These sites play a pivotal role in the regulation of the activity of the receptor (see below).

Results of recent studies using co-immunoprecipitation of differently tagged TRPV1 molecules indicate that TRPV1s are arranged into oligomers to form functioning receptors (Kedei et al., 2001; Kuzhikandathil et al., 2001). These studies also revealed that the predominant form of the functioning TRPV1 is probably tetrameric. As the physiological and pharmacological characteristics of the native and heterologously expressed TRPV1 are very similar (Caterina et al., 1997; Nagy and Rang, 1999), it has been believed that TRPV1s are arranged as homotetramers. However, recently, it has been shown that TRPV1 co-immunoprecipitates with another TRPV molecule, TRPV3, when human embryonic kidney 293 (HEK293) cells are co-transfected with both TRPV1 and TRPV3 (Smith et al., 2002). The co-precipitation was shown to depend on the presence of TRPV3 in the immune complex, and the result of a specific interaction between TRPV1 and TRPV3. Co-transfection of HEK293 cells with TRPV1 and TRPV3 also showed that TRPV3 increases the heteromer's response to capsaicin. The heteromeric structure of the capsaicin receptor is particularly interesting as native TRPV1 might form heteromers with other TRP channels too. These TRPV1-containing hetero(tetra)mers probably have different sensitivity. This assumption is supported by our previous finding that native capsaicin receptors expressed by cultured primary sensory neurons are heterogeneous in their sensitivity to different stimuli at the single channel level (Fig. 2C-E) (Nagy and Rang, 1999).

Recent findings suggest that the capsaicin receptor, similarly to other TRP proteins, for example the one involved in phototransduction in Drosophila, is arranged in major molecular complexes. The TRP complexes are called transducisomes (Vennekens et al., 2002), which, in addition to the TRP protein, contain scaffolding proteins, receptors, such as the high affinity neurotrophic factor receptor, tyrosine kinase B, enzymes including phospholipase C (PLC) and PKC (Vennekens et al., 2002). Chuang et al.'s (2001a,b) findings on HEK293 cells co-transfected by TRPV1 and the high affinity receptor for nerve growth factor (NGF) tyrosine kinase A (trkA) receptor show that TRPV1 co-immunoprecipitates with trkA. Moreover, the immunoprecipitate from the co-transfected HEK293 cells also contains the γ isoform of PLC. The data that reduction of phosphatidylinositol-4,5-bisphosphate (PtdIns(4,5)P_2) level in the plasma membrane increases the activity of TRPV1 (Chuang et al., 2001b) suggest that PtdIns(4,5)P_2 must also be a member of the capsaicin receptor "transducisome". Indeed, recent findings from Prescott and Julius (2003) show that PtdIns(4,5)P_2 binds to TRPV1 and this binding regulates the activity of the capsaicin receptor. In addition to trkA, PLCγ and PtdIns(4,5)P_2, PKA, PKC and calmodulin are also, though probably only transiently, members of the capsaicin receptor complex. Rathee et al. (2002) have reported that the catalytic subunit of PKA translocates to the cytoplasmic membrane following adenylyl cyclase activation. Both α and ε PKC isoenzymes have also been shown to translocate to the cytoplasmic membrane during PKC activation (Cesare et al., 1999; Olah et al., 2002). Recently, Numazaki et al. (2003) and Rosenbaum et al. (2004) have reported that calmodulin, in a Ca^{2+}-dependent manner also binds transiently to TRPV1. The composition of the capsaicin receptor molecular complex seems to be important in the regulation of the activity of the receptor as while activation of trkA and PLC, and translocation of PKA, PKCα and PKCε increases, PtdIns(4,5)P_2-binding decreases the activity of the receptor. The transient calmodulin binding, on the other hand, seems to be

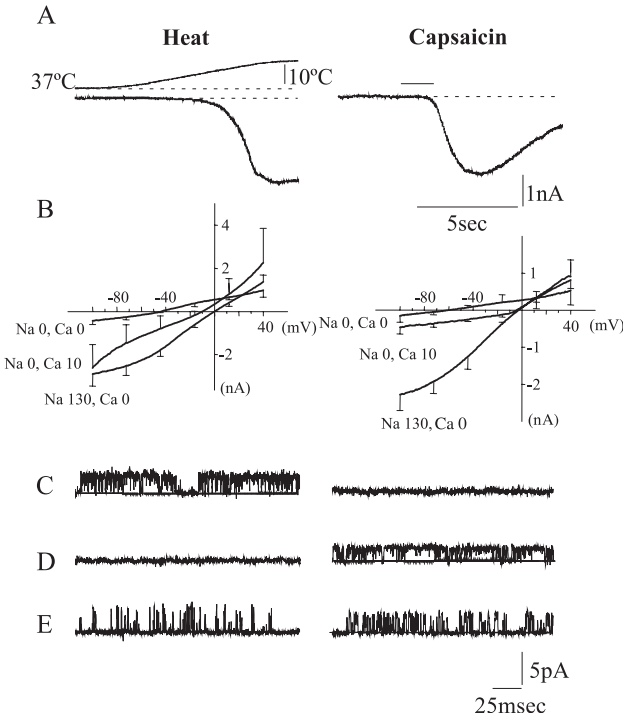

Fig. 2. Noxious heat- and capsaicin-evoked whole-cell (A) currents and their *I–V* relationships measured at different ionic compositions of the extracellular solution (B), and noxious heat- and capsaicin-evoked single channel recordings in inside–out patches (C, D, E) from adult rat cultured primary sensory neurons. (A) Ramp noxious heat stimulation from 37 to 52 °C (upper recording) evokes an inward current in a neuron. The holding potential was −60 mV. The extra- and intracellular solutios were (in mM) NaCl 130, KCl 10, $MgCl_2$ 1.26, $CaCl_2$ 1.26, HEPES 10, glucose 10, and NaCl 10, KCl 130, $MgCl_2$ 1.26, EGTA 1, HEPES 10, respectively. Capsaicin also evokes inward current in the same cells. (B) Averaged *I–V* relationships of noxious heat- and capsaicin-evoked currents. KCl in the pipettes in these experiments was replaced by CsCl. In experiments with zero sodium in the extracellular solution, NaCl was replaced by equimolar *N*-methyl-D-glucamine$^+$. Patches respond differently to noxious heat stimulation and capsaicin application. While 10–15% of the patches taken from small diameter neurons respond either to noxious heat stimulation (C) or capsaicin application (D), only ~5% of them are responsive to two both stimuli (E). The bath- and pipette solutions contained (in mM) K-aspartate 115, KCl 15, $MgCl_2$ 1.26, EGTA 1, HEPES 10, glucose 10, and NaCl 130, KCl 10, $MgCl_2$ 1.26, $CaCl_2$ 1.26, HEPES 10, respectively. The holding potential was 60 mV.

responsible for the capsaicin-receptor activity-induced inhibition, known as desensitisation of the receptor (Numazaki et al., 2003).

Recent studies revealed that two synaptic vesicle proteins, snapin and synaptotagmin IX also interact with TRPV1 (Morenilla-Palao et al., 2004). The interaction with the synaptic vesicle proteins seems to be also temporal, and it is probably not involved in the formation of the transducisome as both synaptic vesicle proteins bind to TRPV1 only in the cytoplasm. However, their interactions seem to be pivotal in the trafficking and cytoplasmic membrane expression of TRPV1.

Electrophysiological characterisation in expression systems revealed that TRPV1 forms a non-selective cationic-channel, which in addition to vanilloids, such as capsaicin and the ultrapotent vanilloid, resiniferatoxin can also be activated by heat above ~42 °C, protons and ethanol (Caterina et al., 1997; Trevisani et al., 2002). These studies showed that the TRPV1-mediated current has a substantial and characteristic Ca^{2+} component and a distinctive outward rectification below 0 mV (Fig. 2). The characteristics of TRPV1-mediated current recorded in different expression systems closely resemble those mediated by the native capsaicin receptor expressed in primary sensory neurons (Caterina et al., 1997; Nagy and Rang, 1999). Recent finding showed that depolarisation enhances the TRPV1-mediated current indicating that the activity of the channel is voltage-dependent and that depolarisation and agonists act in a synergistic fashion (Ahern and Premkumar, 2002).

Co-application of different agonists also results in potentiation of responses (Tominaga et al., 1998). Interestingly, the potentiation seems to be mediated by ligand binding-induced decrease of the heat threshold of the molecule (Tominaga et al., 1998). The Q_{10} of the cooling-evoked decrease of the capsaicin-induced current is similar to that of voltage-gated currents (Babes et al., 2002; Matteson and Armstrong, 1982). Based on these features, the capsaicin receptor has been called a stimulus integrator (Tominaga et al., 1998).

Since the identification of the capsaicin receptor, the number of putative endogenous TRPV1 activators has exponentially increased. While some of the activators induce TRPV1-mediated currents, others, instead of opening the ion-channel, produce allosteric modulation. In general, the endogenous activators could be divided into two groups: those, which bind to, and those, which induce post-translational modification of TRPV1. Interestingly, the effect of the majority of these activators is similar to that of the exogenous ones; they seem to activate TRPV1 through reducing the heat threshold of the molecule.

A large body of evidence indicates that post-translational modifications of TRPV1, such as PKA-, PKC- and CaMkII-mediated phosphorylation of, and PtdIns(4,5)P_2 hydrolysis from, TRPV1 increase the activity of the capsaicin receptor. The PKA-mediated phosphorylation of the capsaicin receptor was first reported to mediate the sensitising effect of the inflammatory mediator, prostaglandin E_2 on capsaicin-induced responses (Lopshire and Nicol, 1998). Later, PKA activation was shown to increase the response of the capsaicin receptor to other exo- and endogenous activators (De Petrocellis et al., 2001; Rathee et al., 2002) and to be involved in NGF-evoked, and $mglu_5$-mediated increase in capsaicin-induced responses (Bonnington and McNaughton, 2003; Hu et al., 2002; Shu and Mendell, 2001). It has been reported that PKA activation reduces the heat-threshold of the capsaicin receptor, though the reduction is rather modest (from ~43 to 41.5 °C; Rathee et al., 2002). Recent findings suggest, however, that the PKA-mediated phosphorylation of

TRPV1 produces the sensitisation effect through the reduction of desensitisation (Bhave et al., 2003; Mohapatra and Nau, 2003).

PKC-mediated phosphorylation of TRPV1 has been shown to activate the receptor on its own and to be involved in the sensitising effect of some inflammatory mediators, such as bradykinin and ATP (Cesare et al., 1999; Cesare and McNaughton, 1996; Premkumar and Ahern, 2000; Tominaga et al., 2001). The direct PKC activation-evoked channel opening was thought to be produced by reduction in the heat-threshold of the molecule (Premkumar and Ahern, 2000). However, recent data show that phorbolesters, which had been used to activate PKC, bind to and activate TRPV1 directly (Bhave et al., 2003). Nevertheless, PKC-mediated phosphorylation induced either by bradykinin or ATP indeed reduces the heat-threshold of the receptor from ~42 to ~35 °C (Liang et al., 2001; Sugiura et al., 2002; Tominaga et al., 2001). Reports on PKC-mediated phosphorylation suggest that different pathways might activate different PKC isoenzymes. While activation of the bradykinin B_2 receptor results in the activity and translocation of PKCε to the cytoplasmic membrane (Cesare et al., 1999) phorbolesters activate, and induce translocation of PKCα (Olah et al., 2002).

Although the expression of CaMkII in TRPV1-positive primary sensory neurons has been reported previously (Carlton and Hargett, 2002; Ichikawa et al., 2004) the role of CaMkII-mediated phosphorylation of TRPV1 has just started to clear up. Bonnington and McNaughton (2003) found that inhibition of CaMkII reduces the NGF-evoked sensitisation of capsaicin-evoked responses in primary sensory neurons. Most recent data show that TRPV1 must be phosphorylated by CaMkII before the receptor is activated by any activator (Jung et al., 2004). Furthermore, these authors found that in contrast to CaMkII-mediated phosphorylation of TRPV1, dephosphorylation of the molecule by calcineurin induces desensitisation of the receptor. Thus, Jung et al. (2004) have proposed that CaMkII-mediated phosphorylation and calcineurin-mediated dephosphorylation of TRPV1 can control the activation/desensitisation states of the capsaicin receptor dynamically. These findings are in agreement with our recent unpublished observation that inhibition of CaMkII activity significantly reduces capsaicin-evoked currents in cultured primary sensory neurons. We also found that inhibition of PKA and PKC activity blocks capsaicin-evoked responses in cultured primary sensory neurons (Sathianathan et al., 2003). Taken together, these data indicate that constitutional activity of protein kinases is necessary to keep the capsaicin receptor in a responding configuration.

Phospholipase C seems to be another regulator of capsaicin receptor activity through removing PtdIns(4,5)P_2 from TRPV1. Activation of PLC either through trkA, bradykinin B_2 or $mglu_5$ receptors enhances the capsaicin receptor-mediated responses (Chuang et al., 2001b; Hu et al., 2002). Similarly to PKA- and PKC-mediated phosphorylation of TRPV1, PLC activation also significantly reduces the heat threshold of the receptor (Chuang et al., 2001b; Prescott and Julius, 2003). Thus, bradykinin can decrease the heat threshold of TRPV1 through at least two mechanisms: PKC-mediated phosphorylation and PLC-mediated PtdIns(4,5)P_2 hydrolysis (Cesare et al., 1999; Cesare and McNaughton, 1996; Chuang et al., 2001b). Similarly to the inhibition of PKA and PKC, inhibition of PLC also blocks capsaicin-evoked responses in cultured primary sensory neurons indicating that constitutional activity of PLC is also necessary to maintain the responding configuration of the capsaicin receptor (Sathianathan et al., 2003).

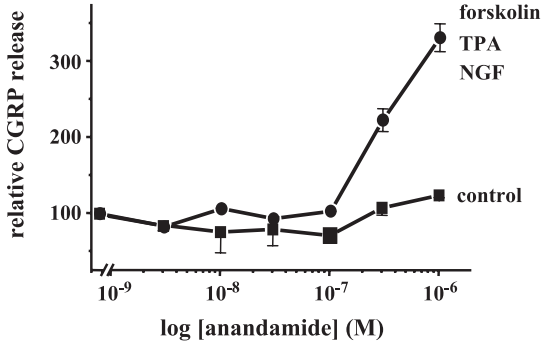

Fig. 3. Concentrationresponse curve of anandamide on CGRP release from adult rat cultured primary sensory neurons kept in culture medium for 36 h after plating without nerve growth factor. Activation of PKA, PKC and PLC by forskolin, TPA and NGF results in hugely increased anandamide-evoked CGRP release at 300 nM and 1 μM. Modified from figure 3C, Ahluwalia et al., Eur. J. Nuerosci. 17:2611-2618. Copyright 2004 by Blackwell Publishing.

The already known putative endogenous TRPV1 activators, which bind to the receptor include protons, ATP, *N*-arachidonoyl-ethanolamine (anandamide), *N*-arachidonoyl-dopamine, *N*-oleoyldopamine, lipoxygenase products, such 12- and 15(*S*)-hydroperoxyeicosatetraenoic acid (12-(*S*)-HPETE and 15-(*S*)-HPETE), 5- and 15-(*S*)-hydroxyeicosatetraenoic acids (5-(*S*)-HETE, 15-(*S*)-HETE) and leukotriene BLT (Caterina et al., 1997; Chu et al., 2003; Huang et al., 2002; Hwang et al., 2000; Kwak et al., 2000; Shin et al., 2002; Zygmunt et al., 1999). All of these endogenous compounds induce capsaicin receptor-mediated inward currents both in recombinant TRPV1-expressing cells and in the native capsaicin receptor-expressing primary sensory neurons. However, both the potency and efficacy of these agents are rather low, and neither of these ligands is believed to induce opening of the ion channel in vivo on their own even at their highest tissue concentrations. Nevertheless, it seems that several ligands are co-released in pathological conditions, and they can act in a synergistic manner. While some of the putative endogenous activators, such as protons and ATP are released from the damaged tissues, others, such as anandamide and the lipoxygenase products can be produced by capsaicin-sensitive primary sensory neurons themselves when activated (Ahluwalia et al., 2003b; Shin et al., 2002). In this respect, anandamide is particularly interesting as it is also

an endogenous ligand of the inhibitory cannabinoid 1 (CB_1) receptor (Devane et al., 1992), which is expressed by all TRPV1-expressing cultured dorsal root ganglion neurons (Ahluwalia et al., 2000). We have shown recently that anandamide, by activating the capsaicin and CB_1 receptor, can regulate the activity and excitability of capsaicin-sensitive primary sensory neurons (Fig. 3) (Ahluwalia et al., 2003a).

In addition to agents, which activate the capsaicin receptor by binding to TRPV1, some other ligands, such as NGF (Shu and Mendell, 2001) prostaglandin E_2 (Lopshire and Nicol, 1998), oestrogen (Schroder et al., 2003), glutamate (Hu et al., 2002), ATP (Tominaga et al., 2001) and ligands of the protease receptor 2 (Kawao et al., 2004) activate their own receptors and in addition to other effects contribute to capsaicin receptor activation by inducing sensitisation through post-translational changes. However, the inflammatory mediator, bradykinin that does not bind to TRPV1 either has been suggested to be a de facto TRPV1 agonist as it has been hypothesised that bradykinin activates primary sensory neurons exclusively through bradykinin B_2 receptor-mediated activation of TRPV1 (Liang et al., 2001; Reeh and Petho, 2000). Indeed, the capsaicin receptor antagonist, capsazepine significantly reduces the bradykinin-evoked action potential generation in capsaicin-sensitive vagal afferents (Carr et al., 2003). However, the relative number of bradykinin-responsive fibres and the frequency of action potentials are similar in TRPV1 knock-out and wild-type mice (Kollarik and Undem, 2004) indicating that, while bradykinin can indeed induce activity in TRPV1, the capsaicin receptor is not essential for bradykinin-evoked activity of capsaicin-sensitive primary afferents.

Identification the molecular mechanisms involved in the activation of TRPV1 is important in designing drugs controlling the activity of the capsaicin receptor. Molecular mapping has revealed the function of several TRPV1 residues (Fig. 1). Studies on chimeras of TRPV1s cloned from capsaicin-sensitive and insensitive species, such as rat or human, and chicken or rabbit, respectively, and on mutated TRPV1s show that intracellular/intramembranous residues in and adjacent to the 3rd and 4th transmembrane domains (Y511 and T550) are responsible for binding of capsaicin to TRPV1 (Gavva et al., 2004; Jordt and Julius, 2002). Binding of other vanilloids such as resiniferatoxin requires the presence of methionine at position 547 (Gavva et al., 2004). These residues are also responsible for the binding of endogenous ligands, such as anandamide, *N*-arachidonoyl-dopamine or *N*-oleoyldopamine (Gavva et al., 2004; Jordt and Julius, 2002). Moreover, these residues are involved in the binding of competitive antagonists, such as capsazepine (Gavva et al., 2004; Phillips et al., 2004). Studies on chimeras of rat TRPV1 and TRPV2, a capsaicin non-sensitive but noxious heat-sensitive TRPV1 homologue (Caterina et al., 1999) and on TRPV1 with various deletions of the C-terminus showed that residues in both the C- and N-termini modify capsaicin-sensitivity and binding (Jung et al., 2002;Vlachova et al., 2003).

While capsaicin interacts with TRPV1 at an intracellular/intramembrane site(s), protons bind to an extracellular site of the molecule (Tominaga et al., 1998). However, different amino acids seem to be responsible for proton-induced opening of the ion-channel and potentiation of responses evoked by other ligands; amino acid at position 600 determines potentiation (Jordt et al., 2000), while amino acid at position 648 is responsible for proton-induced opening (Jordt et al., 2000).

Residues responsible for heat-detection and setting the heat threshold of the molecule seem to be dispersed. As mentioned both phosphorylation and PtdIns(4,5)P_2 removal reduce the heat threshold. The most important residues for PKA- and PKC-mediated phosphorylation-evoked sensitisation are S116 and T370, and S800, respectively; however, phosphorylation of other residues also evoke the responsiveness of the receptor (Bhave et al., 2003; Mohapatra and Nau, 2003). On the other hand, R785 and K788 seem to be responsible for PtdIns(4,5)P_2-binding (Prescott and Julius, 2003).

Residues involved in desensitisation are also worth to note. The high Ca^{2+}-permeability of the capsaicin receptor, which is important in the development of desensitisation is determined by Y671 located on the 6th transmembrane domain. The CaMkII-calcinuerin-mediated regulation of TRPV1 desensitisation involves amino acids S502 and T704 (Jung et al., 2004).

3. TRPV1 expression

Recent findings indicate that TRPV1 is expressed in at least three cellular compartments; in the cytoplasmic membrane, in the endoplasmic reticulum and in the cytoplasmic vesicles (Guo et al., 1999; Morenilla-Palao et al., 2004). While TRPV1s in the cytoplasmic membrane are responsible for the TRPV1-mediated effects, such as inward currents or transmitter release, those in the cytoplasmic vesicles seem to serve as a reserve, which can be quickly translocated to the cytoplasmic membrane, for example following PKC activation (Morenilla-Palao et al., 2004). The role of TRPV1 expressed by the endoplasmic reticulum is not clear. The finding that activation of these receptors by capsaicin or resiniferatoxin evokes Ca^{2+} mobilisation from intracellular stores shows that these receptors are also functional and they might be involved in the regulation of Ca^{2+} homeostasis (Karai et al., 2004; Marshall et al., 2003).

Results of radioactive ligand-biding, reverse transcription polymerase chain reaction (RT-PCR), in situ hybridisation, Western-blotting, immunohistochemical staining and functional studies show that TRPV1, in addition to a subpopulation of primary sensory neurons, is expressed by various neurons and non-neuronal cells. However, some of the results are dubious and it is not clear whether TRPV1s

are functional in all the cells where their expression has been shown. Regarding primary sensory neurons, TRPV1 is expressed by 1/3–1/2 of dorsal root and trigeminal ganglion neurons (Ahluwalia et al., 2000; Guo et al., 1999; Ichikawa and Sugimoto, 2004; Michael and Priestley, 1999). In agreement with the putative role of TRPV1 in nociception, the great majority of the TRPV1-expressing cells belongs to small, nociceptive cells expressing substance P and calcitonin gene-related peptide, or binding site for the isolectin, IB4. Both somatic and visceral primary afferents express TRPV1 and the molecule is expressed by both the spinal and peripheral terminals (Avelino et al., 2002; Guo et al., 1999; Valtschanoff et al., 2001). Interestingly, it seems that instead of the TRPV1 protein, the mRNA of the receptor is transported to the terminals and the translation occurs there (Tohda et al., 2001). In addition to dorsal root ganglion and trigeminal ganglion neurons, vagal afferents in jugular and nodose ganglion neurons also express TRPV1 (Ichikawa and Sugimoto, 2003) and similarly to dorsal root ganglion and trigeminal ganglion neurons TRPV1 is also expressed by both the peripheral and central terminals (Ward et al., 2003).

In the skin, TRPV1-expressing fibres can be found in the dermis, along the epidermal/dermal junction and epidermis (Guo et al., 1999). Although the capsaicin receptor is associated with nociception, thus with C-type primary sensory neurons terminating in free nerve endings at the periphery, in the skin, TRPV1-immunopositive fibres have been found to innervate Meissner corpuscules (Pare et al., 2001). This finding indicates that Meissner corpuscules might also be involved in nociception.

In viscera, TRPV1 immunopositive fibres were observed both in the mucous membrane, submucous and muscular layer (Avelino et al., 2002; Ward et al., 2003). TRPV1 fibres accompany blood vessels in all layers of viscera. In the bladder, TRPV1-expressing fibres are in close vicinity with the basal cells of the urothelium. Some fibres occasionally enter the transitional epithelium. TRPV1-immunopositive fibres in the muscular layer seem to establish contacts with smooth muscle cells (Avelino et al., 2002). In the gastrointestinal tract, TRPV1 positive fibres of sensory origin distribute within the myenteric and submucous plexus where they establish synaptic connections with enteric neurons. Some of the intrinsic enteric neurons in the myenteric plexi, particularly in the guinea pig ileum and colon seem to express TRPV1 (Anavi-Goffer and Coutts, 2003; Poonyachoti et al., 2002). In the muscular layer, TRPV1-expressing fibres seem to contact interstitial cells of Cajal. Unidentified round TRPV1-immunopositive cells were also found in the villi of the small intestine (Ward et al., 2003). Peripheral terminals of TRPV1-expressing vagal afferents innervate however only the gastric mucosa (Ward et al., 2003).

Recent findings indicate that TRPV1 is expressed in many areas of the central nervous system. In the spinal cord, TRPV1 has been shown on postsynaptic structures with spinal cord origin (Valtschanoff et al., 2001). Binding and in-situ hybridisation studies on wild-type and TRPV1 knock-out mice confirmed the results of previous findings on the widespread expression of TRPV1 in the brain (Mezey et al., 2000; Roberts et al., 2004). These data show TRPV1 mRNA and/or protein and vanilloid-bindings sites in the olfactory nuclei, layers 3 and 5 of the cerebral cortex, dentate gyrus, central amygdala, habenula, striatum, centromedian and paraventricular thalamic nuclei, hypothalamus, substantia nigra, reticular formation, periaqueductal grey, superior colliculus, locus coeruleus, inferior olive and cerebellar cortex. Interestingly, neonatal capsaicin treatment does not deplete TRPV1 mRNA in the central nervous system, though results of some pharmacological studies indicate that at least some of the TRPV1s expressed in the brain must form functional capsaicin receptor (Mezey et al., 2000). Nevertheless, further studies are needed to verify the expression and functionality of TRPV1 in the brain.

TRPV1 expression has also been demonstrated in the inner ear, where TRPV1-expressing cells include inner and outer hair cells, inner and outer pillar cells, Hensen's cells, spiral ganglion neurons, Scarpa's ganglionic neurons and satellite cells (Balaban et al., 2003; Zheng et al., 2003). The findings that both capsaicin and resiniferatoxin increased the threshold for auditory nerve compound action potential generation and reduced the magnitude of cochlear microphonic and electrically evoked otoacoustic emissions suggest that capsaicin receptors are functional in the inner ear (Zheng et al., 2003).

In addition to neurons and cells in the inner ear, other cells of ectodermal origin also seem to express functional capsaicin receptors. Inoue et al. (2002) and Southall et al. (2003) have reported that a proportion of human cultured keratinocytes express TRPV1 and capsaicin induces Ca^{2+} influx into a subpopulation of these cells. Interestingly, other heat-sensitive TRP channels are also expressed by keratinocytes (Chung et al., 2003; Peier et al., 2002).

Some cells with endodermal origin also express TRPV1. Kato et al. (2003) have shown TRPV1 protein and mRNA expression in cultured rat gastric epithelial cells, though it is not clear whether all the cells or just a subpopulation of them express TRPV1. Kato et al. (2003) have also shown that capsaicin does not induce desensitisation or degeneration in gastric epithelial cells. Epithelial cells in the urinary bladder have also been shown to express TRPV1 both at mRNA and protein level (Birder et al., 2001). Immunohistochemical reactions revealed TRPV1 expression both in the basal and superficial layers of the urothelium. Both capsaicin and resiniferatoxin induce TRPV1-mediated increase in intracellular calcium concentration indicating that the receptors are functional. Similarly to gastric epithelial cells, however, capsaicin does not induce the characteristic vanilloid-evoked desensitisation in epithelial cells of the urothelium either. This is an important difference between

neurons and epithelial cells expressing TRPV1, which requires further studies.

Cells of mesodermal origin have also been reported to express TRPV1. Birder et al. (2001) have reported that bladder smooth muscle cells express TRPV1. However, these findings have not been confirmed either by showing TRPV1 protein expression or capsaicin-induced responses in isolated smooth muscle cells. Cardiomyocytes seem to express TRPV1 transiently during the development in rats between E14 and P30 (Dvorakova and Kummer, 2001). Whether or not these receptors are functional also remains to be elucidated. TRPV1 expression was also shown in interstitial cells of the urinary bladder and the prostate recently by using immunohistochemical staining (Ost et al., 2002; Van Der Aa et al., 2003). However, the methods used by these authors suggest that some of the stainings they found must be artefact.

Concentration-dependent anandamide-induced cell-death in cervical cancer cell lines suggests that TRPV1 may be ectopically expressed on these cells (Contassot et al., 2004). RT-PCR study on cervical cancer biopsies showed that TRPV1 is expressed by these cells in vivo, as well.

4. TRPV1 in pathological conditions

4.1. Heat hyperalgesia

The capsaicin receptor has been associated with heat hyperalgesia for a long time. Capsaicin induces burning pain, similar to that observed often in inflammation. Locally applied capsaicin reduces inflammation-evoked heat hyperalgesia suggesting that the capsaicin receptor plays an important role in the development of inflammatory heat hyperalgesia (Coderre et al., 1986). Studies on TRPV1 knock-out mice proved that the expression and activity of the capsaicin receptor is essential for the development of inflammatory heat hyperalgesia. While inflammation of peripheral tissues reduced the threshold for heat-evoked pain-related responses in wild-type mice, this reduction was missing in TRPV1-deficient mice (Caterina et al., 2000; Davis et al., 2000). Two main types of mechanisms underlying TRPV1 activation in inflammation have been postulated. According to the first hypothesis, inflammatory mediators, such as bradykinin, NGF, ATP or prostaglandin E2, produced and released during inflammation activate their respective receptors expressed by the peripheral terminals of primary sensory neurons. Activation of these receptors induces activation of intracellular messengers, such as PKA, PKC and PLC, which open the TRPV1 ion-channel through reducing the heat threshold of the receptor. While under in vitro conditions PKC-mediated phosphorylation of TRPV1 and PtdIns(4,5)P_2 hydrolysis seem to reduce the threshold below the body temperature (Chuang et al., 2001b; Liang et al., 2001; Prescott and Julius, 2003; Sugiura et al., 2002; Tominaga et al., 2001), no in vivo data exist to support that such change is sufficient to produce heat hyperalgesia. The second hypothesis proposes that endogenous ligands activate the receptor. This proposal is supported by findings that capsazepine, the competitive capsaicin antagonist significantly reduces inflammatory heat hyperalgesia (Kwak et al., 1998; Walker et al., 2003). However, as mentioned above the efficacy and potency of the known endogenous ligands are low and it has been debated whether in vivo concentrations can be high enough to activate TRPV1. Nevertheless, different activators of TRPV1, such as heat, H^+, post-translational changes and various ligands potentiate each other's effect (Bonnington and McNaughton, 2003; De Petrocellis et al., 2001; Premkumar and Ahern, 2000; Shu and Mendell, 2001; Tominaga et al., 1998; Tominaga et al., 2001; Price et al., 2004). Our recent finding on anandamide-evoked TRPV1 activation suggests that such concerted action of various activators could be responsible for TRPV1 activation in inflammatory conditions (Fig. 3) (Ahluwalia et al., 2003a). This assumption is supported by data showing that the concentration of endogenous TRPV1 ligands, such as anandmaide is increased in inflamed tissues (Avelino et al., 2003; McVey et al., 2003) and that inflammation activates PKCε (Zhou et al., 2003). In addition to the concerted action of activators, upregulation of TRPV1 expression also contributes to the development of inflammatory heat hyperalgesia (Amaya et al., 2003; Ji et al., 2002; Zhou et al., 2003). It has been found that the proportion of TRPV1-expressing unmyelinated axons increased in the inflamed tissues and that inflammation increases the number of TRPV1-expressing primary sensory neurons in dorsal root ganglia (Amaya et al., 2003; Zhou et al., 2003). Inflammatory heat hyperalgesia develops both in somatic and visceral tissues and the finding that in vulvodynia the number of TRPV1 immunopositive fibres is increased suggests that the capsaicin receptor also plays some role in the development of visceral inflammatory heat hyperalgesia (Tympanidis et al., 2004).

In addition to inflammation, heat hyperalgesia also develops in other pathological conditions, such as peripheral nerve injury, diabetes and herpes simplex. Nerve injury induces downregulation of TRPV1 expression in the perikarya of injured primary sensory neurons (Michael and Priestley, 1999) and the activity of PKCε (Zhou et al., 2003). These findings together with the lack of reduction of nerve injury-induced heat hyperalgesia in TRPV1−/− animals in comparison to the wild-type mice suggest that TRPV1 is not involved in the development of peripheral nerve injury-induced heat hyperalgesia. However, increased TRPV1 expression in the perikarya of uninjured primary sensory neurons supports the assumption that TRPV1 expression and activation is involved in the development of heat hyperalgesia after peripheral nerve injury (Fukuoka et al., 2002; Hudson et al., 2001). Clearly, further studies are needed to elucidate the role of TRPV1 and the mechanisms involved in peripheral nerve injury-induced heat hyperalgesia.

Diabetic neuropathy also features heat hyperalgesia. Recent findings that intrathecal injection of TRPV1 antiserum significantly reduces heat hyperalgesia in streptozotocin-injected rats indicate that TRPV1 activation at the spinal terminals of primary afferents is involved in the development of burning pain in diabetes (Kamei et al., 2001). A mechanism for the development of TRPV1-mediated heat hyperalgesia was suggested by our recent study. We found that the insulin receptor is co-expressed with TRPV1 in a subpopulation of primary sensory neurons and that insulin activates the capsaicin receptor (Sathianathan et al., 2003). These results indicate that insulin-evoked TRPV1 activation might play a role in the development of heat hyperalgesia in hyperinsulinaemic conditions, such as the initial phase of type 2 diabetes, characterised by increased insulin blood level and distal symmetric sensory polyneuropathy (e.g. "gloves and socks" type burning pain) (Delaney et al., 1994; Russell and Feldman, 2001).

It has been reported recently that the development of herpes simplex-induced heat hyperalgesia also depends on TRPV1 activation. Hunsperger and Wilcox (2003) found that, following the establishment of latent virus infection in cultured primary sensory neurons, capsaicin application dose-dependently reactivates the virus. In addition to capsaicin, heat also reactivates the latent infection. The reactivation is TRPV1-mediated and depends on Ca^{2+} influx.

4.2. Brain

While vanilloids have been shown to modify activity in different areas of the central nervous system (Al Hayani et al., 2001; Hajos and Freund, 2002), very little is known about the physiological and pathophysiological role of TRPV1 in brain. A recent finding suggests that activation of TRPV1 in the brain might be involved in the development of motor disorders. Anandamide has been found to induce reduction in ambulation, stereotypies and exploration (De Lago et al., 2004). The anandamide-evoked effect can be significantly reduced by capsazepine. Moreover, capsazepine reverses the anandamide-evoked reduction of the 3,4-dihydroxyphenylacetic acid content of the caudate–putamen, suggesting that TRPV1 activity decreases dopamine turnover in the basal ganglia. Furthermore, anandamide also decreases the stimulated dopamine release from nigrostriatal terminals.

4.3. Inner ear

Role of TRPV1 in the development of diseases, such as hyperacusis, tinnitus, vestibular hypersensitivity and some forms of episodic vertigo, has been suggested recently (Balaban et al., 2003). The proposal is based on the findings that spiral and vestibular ganglionic cells, in addition to TRPV1 also express 5-lipoxygenase, the product of which has been suggested to be endogenous TRPV1 ligand and that increased lipoxygenase activity produces tinnitus. As capsaicin application to the scala tympany indeed induces elevation of the threshold of cochlear compound action potential generation, TRPV1 might be involved in the development of hyperacusis (Zheng et al., 2003).

4.4. Skin

The expression of TRPV1 in keratinocytes suggests that TRPV1 might be involved in the development of skin disorders. Capsaicin, through TRPV1 activates cyclooxygenase-2, in a Ca^{2+}-dependent manner and induces the release of interleukin-8 and prostaglandin E_2 (Southall et al., 2003). It has been speculated that prostaglandin E_2 released from keratinocytes may contribute to the activation of primary sensory neuronal terminals in the dermis (Southall et al., 2003).

4.5. Gastrointestinal tract

As mentioned above, various structures seem to express TRPV1 in the gastrointestinal tract; peripheral terminals of primary and vagal sensory neurons, intrinsic enteric neurons in the myenteric plexi and gastric epithelial cells (Anavi-Goffer and Coutts, 2003; Kato et al., 2003; Poonyachoti et al., 2002; Ward et al., 2003). Regarding the stomach and duodenum, one of the most prominent functions of TRPV1-expressing sensory nerves is the maintenance of the integrity of the tissues against aggressive compounds, such as protons and activated enzymes (Holzer, 2002). A major barrier protecting gastric and duodenal tissues is a viscous mucus layer covering the entire luminar surface of the stomach and duodenum. Activation of TRPV1-expresing primary afferents has been shown to contribute to the thickening of this protective layer (Akiba et al., 2001). While selective elimination of capsaicin-sensitive nerve fibres aggravates the chemically induced mucosal damage in the stomach (Szolcsányi and Mozsik, 1984), low concentrations of the TRPV1 ligands, such as capsaicin, acids and alcohol results in increased resistance of the gastric mucosa towards chemical injury (Holzer et al., 1990; Yamamoto et al., 2001). Capsaicin-sensitive primary afferents seem to contribute to the tissue protection through more than one mechanism. On the one hand, capsaicin induces hyperaemia through vasorelaxation produced by calcitonin gene-related peptide (CGRP) release from capsaicin-sensitive primary sensory fibres (Holzer and Guth, 1991), which increases the metabolic activity of the cells. On the other hand, the capsaicin-induced CGRP release has been shown to activate cyclooxygenase-1 enzymes inducing the production of prostaglandin E_2 (Saeki et al., 2004). This latter compound activates secretory cells, which produce the protective layer (Harada et al., 2003). Recent findings indicate that activation of TRPV1 expressed on gastric epithelial cells may also play some role in the defence mechanism (Kato et al., 2003). Kato et al. (2003) have found that two TRPV1 activators, protons (pH4.0) and alcohol (10%) induces cell

damage, while activators such as the vanilloids, capsaicin (10^{-9}–10^{-6} M) and resiniferatoxin (10^{-12}–10^{-9} M) concentration-dependently prevent the proton and alcohol-evoked effects. These authors have also found that TRPV1 expressed by gastric epithelial cells is 99.8% identical to those cloned by Caterina et al. (1997). These findings indicate that the subtle difference between TRPV1 in primary sensory neurons and in gastric epithelial cells could be enough to produce major differences in sensitivity to, and in the well-described potentiation effect of, various activators. Alternatively, TRPV1s in the epithelial cells and in primary sensory neurons are indeed identical, but the subcellular distribution is different, e.g. in epithelial cells TRPV1 is expressed only on the endoplasmic reticulum and only capsaicin could reach TRPV1 without producing membrane damage. It has been speculated that the direct capsaicin-evoked protective effect on epithelial cells involves Ca^{2+}-dependent activation of cyclooxygenase 1.

TRPV1 expressed by primary sensory neurons in the gastrointestinal tract has also been implicated in the development of inflammation and hyper-motility/hyper-reflexia. It has been shown that substance P is a major player mediating inflammation in the intestines (Pothoulakis et al., 1994). The finding that the TRPV1 antagonist, capsazepine prevents the development of Toxin A-induced inflammation indicates that the capsaicin receptor is involved in the process, and capsaicin-sensitive primary sensory fibres are the major source of substance P (McVey and Vigna, 2001). Recent findings suggest that the endogenous substance activating TRPV1 during ileitis is anandamide (McVey et al., 2003). Anandamide concentration in the inflamed tissues is increased and this endogenous TRPV1 ligand exacerbates ileitis. However, Mang et al.'s (2001) data that anandamide induces acetylcholine release from intrinsic enteric neurons expressing TRPV1 receptors suggest that the capsaicin receptor expressed by neurons in the myenteric plexi might also contribute to the development of enhanced intestinal motility and secretion. It should be noted however, that other groups using different chemicals to induce experimental colitis or enteritis (Evangelista and Tramontana, 1993; McCafferty et al., 1997; Reinshagen et al., 1996) reported a rather accentuated inflammation following ablation of capsaicin-sensitive nerve fibres with systemic capsaicin treatment of adult animals. This effect was explained by the possible protective actions of the sensory neuropeptide, CGRP on the mucous membrane.

Activity of TRPV1 has also been implicated in the development of abdominal pain occurring during irritable bowel syndrome, which is the most common form of the pathological conditions termed functional bowel disorders. Since the pain experienced by the patients is not matched with any detectable structural abnormality by conventional diagnostic methods, the concept of an altered nociceptive function as the main ethiological factor of irritable bowel syndrome-associated pain has been developed (Collins et al., 2001; Hunt and Tougas, 2002). According to the proposed mechanism sensitisation of TRPV1 by a variety of ligands including the protease activated receptor 2 expressed by primary sensory neurons (Coelho et al., 2002; Kawao et al., 2004) and by paracrine/endocrine substances produced by the enterochromaffin (e.g. serotonin) or enteroendocrine (e.g. cholecystokinin) cells underlay the development of abdominal pain in irritable bowel syndrome (Hillsley and Grundy, 1998). Although the involvement of TRPV1 in the development of visceral hyperalgesia has been demonstrated in human (Drewes et al., 2003), the contribution of this mechanism to the pathogenesis of the irritable bowel syndrome is still debated.

The finding that neonatal capsaicin injection significantly reduces both the increase in the biochemical markers, amylase and myeloperoxidase in the serum, and the oedema formation in the parenchyma following the induction of experimental pancreatitis suggests that TRPV1 activity might be involved in the development of the inflammation of this organ (Nathan et al., 2002). Histological investigations also revealed that neonatal capsaicin treatment significantly reduces tissue damage occurring in pancreatitis (Nathan et al., 2002). Since previous observations showed a substantial role for substance P in the pathophysiology of acute pancreatitis, it has been suggested, that substance P release from capsaicin-sensitive sensory fibres is responsible for the development of the neurogenic component of pancreatitis (Bhatia et al., 1998; Grady et al., 2000; Nathan et al., 2001). The mechanism by which capsaicin-sensitive sensory fibres are stimulated is not known, but the involvement of TRPV1 receptor activation was confirmed by showing that capsazepine administration significantly decreases substance P release and alleviates parenchymal damage and myeloperoxidase production in acute pancreatitis (Nathan et al., 2001).

4.6. Urinary tract

The significant role of TRPV1 in bladder disfunction has been well documented. Intravesical application of capsaicin or resiniferatoxin induces reflex activation of the bladder smooth muscle and neurogenic inflammation in the bladder wall (Maggi et al., 1989; Maggi et al., 1984). Two mechanisms underlying the vanilloid-induced increased contractions have been postulated. According to the first hypothesis, capsaicin or resiniferatoxin directly activates capsaicin-sensitive primary sensory neurons in the subepithelial layer of the bladder, which in turn release substance P. Substance P then sensitises smooth muscle cells resulting in increased contractions (Quartara and Maggi, 1998). The second hypothesis is based on the recent finding that TRPV1 is also expressed by epithelial cells of the transitional epithelium, and activation of these TRPV1-expressing cells results in ATP release, which then activates $P2X_3$ receptors expressed by bladder afferents (Birder et al., 2001; Ferguson et al., 1997). Both mechanisms have been

implicated in the development of micturition reflex. Stretching of the bladder wall during bladder filling activates TRPV1-expressing bladder afferents either directly or through the release of ATP from urothelial cells. In both cases, TRPV1 has been thought to act as a mechanotransducer. Caterina (2003) suggested that co-assembly of TRPV1 with mechano-responsive TRP proteins might underlay the mechanosensitivity of the capsaicin receptor in the bladder.

TRPV1-expressing unmyelinated bladder afferents are insensitive to mechanical stimuli, thus, believed not be involved in micturition in naive conditions (De Groat and Yoshimura, 2001). However, TRPV1 knock-out mice have higher frequency of low-amplitude, non-voiding bladder contractions and reduced reflex voiding during bladder filling (Birder et al., 2002) indicating that TRPV1 is involved in the bladder activity not only in inflammatory conditions. Nevertheless, following sensitisation, for example in inflammation or following spinal cord injury, the activity of capsaicin-sensitive fibres is thought to play a key role in the pathological micturition reflex, which is characterised by frequent involuntary voiding (urge incontinence), decreased bladder capacity and occasional ureteral reflux (De Groat et al., 1990; Fowler, 2002). Selective sensory denervation of the bladder elicited by intravesical capsaicin or resiniferatoxin disrupts this overactive spinal reflex, resulting in decreased voiding frequency and increased bladder capacity (Cruz et al., 1997a,b; De Ridder et al., 1997; Silva et al., 2000).

The mechanisms involved in the sensitisation and activation of capsaicin-sensitive bladder afferents has not been elucidated. Inflammatory mediators, such as nerve growth factor released from activated inflammatory cells, have been implicated in the sensitisation (Chuang et al., 2001a; Vizzard, 2000). As mentioned, inflammatory mediators inducing post-translational changes in TRPV1 can reduce the heat threshold of the receptor and contribute to the sensitisation/activation of TRPV1. However, Avelino et al. (2003) have demonstrated recently that cyclophosphamide-induced cystitis, similarly to toxin-A-evoked ileitis (McVey et al., 2003), is accompanied by increased anandamide levels in the bladder. Moreover, these authors have also demonstrated that both exo- and endogenous anandamide enhance bladder reflex activity in a pattern similar to that observed in cyclophosphamide-induced cystitis. These findings suggest that anandamide may be a major activator of TRPV1 in cystitis.

4.7. Airways

The sensitivity of the respiratory tract to capsaicin and other vanilloids is also well documented. Capsaicin-responsive afferents are either superficial fibres terminating in the mucosa or deep pulmonary fibres located in the alveolar septa (Paintal, 1973). The later types of fibres are associated with pulmonary blood vessels. Superficial fibres monitor the chemical environment of the airway mucosa and their activation results in cough, increased mucosal secretion and bronchoconstriction (Coleridge and Coleridge, 1984). The development of these effects involves substance P released from capsaicin-sensitive fibres (Maggi et al., 1991). Inflammation or altered responsiveness of immunocompetent cells located in the mucosa sensitises the mucosal nociceptors, which can significantly amplify the broncho- and secretomotor response leading to the exacerbation of the pathological processes (Undem and Carr, 2001). This mechanism is considered as an important factor in the pathogenesis of asthma.

Deep pulmonary unmyelinated fibres are proposed to participate in the signalling of chemical and circulatory changes in the intersticium of the alveolar septum. Their contribution to the development of broncho-pulmonar diseases is less understood, but they have been shown to be involved both in the sensation of the unpleasant feeling of dyspnoe provoked by congestion in the pulmonary circulation and in the initiation of dry cough (Paintal, 1995).

It has been demonstrated that lipoxygenase products activating TRPV1 are synthesised in various cells, including bronchial epithelial cells (Holtzman, 1992; Shannon et al., 1991), and that eicosanoids are produced following bradykinin B_2 receptor activation in the sensory nerve endings (Shin et al., 2002). Thus, the profound bradykinin-evoked pulmonary effects are presumably mediated at least in part by the eicosanoids–lipoxygenase pathway discussed above. While leukotriene B_4 has been showed to directly activate TRPV1, the potent bronchoconstrictor cysteinyl leukotriene, LTC_4 and its derivatives leukotriene D_4 and leukotriene E_4 seem to act via the cysteinyl-leukotriene receptors in primary sensory neurones (McAlexander et al., 1998; Montuschi et al., 2000). Although Calignano et al. (2000) found that anandamide-induced bronchoconstriction is not sensitive to capsazepine, others found that this effect, although through lipoxygenase products, is mediated by TRPV1 (Craib et al., 2001). The role of anandamide in brochoconstriction is supported by the loss of the anandamide-evoked effect on TRPV1 knock-out mice (Kollarik and Undem, 2004). Activation of TRPV1 either by lipoxygenase- or LTC_4-synthase products has also been implicated in the development of aspirin-sensitive asthma (Sampson et al., 1997; Serhan, 1997).

4.8. Circulation

Sensory fibres innervating the myocardium and forming perivascular plexi of coronary arteries (Franco-Cereceda, 1988; Gulbenkian et al., 1995) express TRPV1 and activation of these capsaicin receptors contributes to the development of the well-known Bezold-Jarisch reflex occurring during arterial injection of capsaicin (Aviado and Guevara, 2001). TRPV1 in perivascular plexi activated by low pH of the ischaemic heart muscle during insufficient coronary circulation (Franco-Cereceda et al., 1993) contrib-

utes also for the development of chest pain and reflectory sympathetic activation (Zahner et al., 2003). Furthermore, TRPV1 expressing sensory fibres seems to contribute to the myocardial protection as the capsaicin receptor both through direct (low pH or anandamide production in ischaemic heart; Epps et al., 1982) and indirect mechanisms (ATP release from damaged cells) is able to detect myocardial damage and initiate an immediate local response through a neurosecretory process (Franco-Cereceda et al., 1993; Kallner et al., 1998; Mair et al., 1990). The cardioprotective effect is thought to be mediated through CGRP and nitric oxide release from capsaicin-sensitive afferents, both of which exert profound cardioprotective effects (Li et al., 1996; Pabla and Curtis, 1996). This assumption is supported by the finding that selective sensory denervation of the heart completely abolishes the protective effect of myocardial preconditioning elicited by high frequency pacing of the heart (Ferdinandy et al., 1997). Interestingly, TRPV1 might also be involved in cardioprotection in toxic myocardial damage as elimination of capsaicin-sensitive afferents results in acceleration in the development of anthracyclin-induced dilatative cardiomyopathy (Katona et al., 2002).

Wang et al. (1998) have demonstrated that after neonatal capsaicin treatment increased sodium intake induces arterial hypertension through restricted sodium excretion in the urine. Alterations in the plasma levels of renin and angiotensin II in capsaicin-treated animals indicate disturbances in the neuro-humoral regulation of the natriuresis (Huang and Wang, 2001; Wang et al., 2001). The involvement of TRPV1 in the prevention of high sodium intake-produced hypertension is supported by the finding that capsazepine significantly elevates the arterial blood pressure in animals on high salt-containing diet (Li and Wang, 2003). It has been shown that a 3-day long high sodium-containing diet significantly elevates the CGRP level in the plasma and TRPV1 expression in the renal medulla and the mesenteric blood vessels (Li and Wang, 2003). Based on these findings, the authors speculate that increased sodium uptake either through increased Na^+ blood level or osmolarity results in tonic activation of TRPV1 and subsequent release of CGRP. The molecular mechanism of this proposed TRPV1 activation, however, needs to be elucidated.

5. Therapeutic implications

The potential therapeutic use of capsaicin-type compounds had not been considered for a long time after the discovery of the selective activating and subsequent desensitising effects of these agents on nociceptive nerve endings (Jancsó and Jancsó, 1949; Szallasi and Blumberg, 1999). The demonstration of selective and long-lasting chemical and thermal analgesia resulting from a single application of capsaicin onto peripheral nerves has led to the suggestion that capsaicin may be considered as a promising tool in relieving certain pains of peripheral origins (Jancsó et al., 1980, 1987a,b; Jancsó and Lynn, 1987). Further studies showed that repeated topical capsaicin application transiently increases the noxious heat threshold and reduces the neurogenic vascular reaction, and that both the nociceptive afferent and the local regulatory efferent functions of the capsaicin-sensitive fibres recover within a few days or weeks after the cessation of the treatment (Carpenter and Lynn, 1981; McMahon et al., 1991; Westerman et al., 1988). Importantly, these studies also showed that topical capsaicin application does not produce trophic lesion of the skin, which occurs often after neonatal capsaicin treatment in rats (McMahon et al., 1991; Jancsó et al., 1980). Soon after these findings preparations containing 0.025–0.075% capsaicin became widely used in the treatment of a number of pathological conditions, such as herpes zoster (Bernstein et al., 1987; Johnson and Whitton, 2004; Westerman et al., 1988), diabetic neuropathy (Spruce et al., 2003; Tandan et al., 1992), notalgia paresthetica (Wallengren and Klinker, 1995), neck-, post-thoracotomy-, post mastectomy- and amputation stump pain, and painful skin tumors (Mathias et al., 1995; Rayner et al., 1989; Watson and Evans, 1992; Wist and Risberg, 1993). Following the successful dermal application, capsaicin and resiniferatoxin were suggested to be used through intravesical instillation to treat inflammatory and spinal cord injury-induced bladder detrusor instability, hyperreflexia and hyperalgesia (Cruz et al., 1997a,b; De Ridder et al., 1997). Recent findings indicate that a single resiniferatoxin instillation indeed significantly reduces the number of urgencies and episodes of incontinence and increases the bladder volume for months without producing significant pain or discomfort (Cruz, 2004; Silva et al., 2000). Intranasal capsaicin application has also been suggested as a novel therapeutic approach in the treatment of cluster headache (Sicuteri et al., 1989). Subsequent studies confirmed the beneficial effect of preventive capsaicin application in the amelioration of the symptoms of headache episodes (Fusco et al., 1994; Marks et al., 1993).

Although topical application of vanilloids onto the skin, mucous membranes or instillation into hollow viscera, such as the urinary bladder exerts a moderate to significant analgesic effect, this route is less effective or inappropriate in relieving deep tissue pain. Recent findings show that administration of vanilloid compounds through alternative routes, such as application of capsaicinoids onto peripheral nerves, or injecting the agent into the epidural or subarachnoid space produce highly effective antinociception. A single application of capsaicin onto a peripheral nerve, which is regarded as a safe and highly specific chemodenervation technique to block the function of nociceptive C-fibres has been demonstrated to produce a selective and long lasting thermal and chemical analgesia confined to the innervation territory of the affected nerve (Fitzgerald and Woolf, 1982; Jancsó et al., 1980). Perineural treatment with capsaicin results in a dose-dependent increase in the threshold of nociceptive reflexes elicited by noxious heat

stimulation and chemical irritants as well as in a partial or complete reduction of the neurogenic inflammatory response (Jancsó et al., 1980, 1987a,b). Although capsaicin is administered at a high concentration (32 mM/l), its effects are highly selective as neither unmyelinated autonomic nor myelinated afferent or motor fibres are affected (Jancsó et al., 1987a,b). Electrophysiological recordings from capsaicin-treated peripheral nerves show a selective loss of nociceptive but not non-nociceptive afferent fibres. The loss is particularly evident among the polymodal nociceptors (Pini et al., 1990). Morphological studies revealed that about 35% of the unmyelinated axons are lost 6–8 weeks after perineural treatment with capsaicin (Jancsó and Lawson, 1990; Pini et al., 1990).

Administration of minute quantities of capsaicin into the spinal or medullar subarachnoid space results in prolonged thermal and chemical hypoalgesia in somatotopically related skin areas (Jancsó, 1981; Yaksh et al., 1979). Light and electron microscopic studies revealed that intracisternal or intrathecal administration of capsaicin results in a massive degeneration of medullary and spinal C-fibre primary afferent terminals without affecting either the structural or biochemical integrity of the perikarya or the local regulatory function of the cutaneous nerve endings (Jancsó, 1981; Palermo et al., 1981). Epidural administration of capsaicin or resiniferatoxin has similar effects; both vanilloids produce long-lasting, segmental analgesia to C-fiber-mediated pain elicited by noxious heat (Eimerl and Papir-Kricheli, 1987; Szabo et al., 1999). Decreased [^{3}H]resiniferatoxin-binding in the spinal cord following epidural capsaicin or resiniferatoxin administration suggests the loss of spinal terminals of capsaicin-sensitive primary sensory neurons (Szabo et al., 1999). These findings indicate that vanilloid compounds may provide effective pain relief through intrathecal and/or epidural administration. This approach may be particularly useful to ameliorate inflammatory and/or cancer pain of abdominal and pelvic origin, which are difficult to relieve with conventional techniques of regional analgesia.

Several mechanisms could contribute to the therapeutic effects of capsaicin and resiniferatoxin. Studies on laboratory animals show that while systemic capsaicin treatment of newborn animals results in a permanent elimination of capsaicin-sensitive spinal and cranial sensory ganglion neurons (Jancsó and Király, 1980; Jancsó et al., 1987a,b), topical capsaicin administration results in temporal, however, extensive loss of peptidergic and non-peptidergic afferent fibres only locally (Dux et al., 2003; Király et al., 1991; Klukovits et al., 2004; Simone et al., 1999). Perineural capsaicin application, on the other hand, apparently produces a permanent loss of capsaicin-sensitive fibres (Dux et al., 1999) . The capsaicin-induced local loss of cutaneous or bladder afferents is causally related to the development of hypoalgesia to noxious mechanical, heat and chemical stimuli and improved bladder functions (Cruz, 2004; Simone et al., 1999). The exact mechanism of capsaicin-induced cell death and permanent sensory neuronal loss is unclear. The massive accumulation of intracellular Ca^{2+} after capsaicin application indicates the involvement of this ion in the degenerative and/or apoptotic processes (Hiura et al., 2002; Jancsó et al., 1984). However, a significant proportion of the cell loss may be due to impaired retrograde transport of trophic factors, particularly to that of NGF (Miller et al., 1982; Jancsó and Lawson, 1990; Schicho et al., 1999). Cruz and his co-workers suggest that this later mechanism might be responsible for the beneficial effects of intravesical capsaicin or resiniferatoxin instillation (Cruz, 2004). As nerve fibre degeneration was not apparent 24 h after capsaicin or resiniferatoxin administration into the urinary bladder these authors argue that the loss of TRPV1 and substance P immunostaining in the bladder are the results of the disappearance of TRPV1 produced by vanilloid binding, and of the subsequent depletion of substance P. Furthermore, they argue that as the transport of NGF that is needed for the transcription of genes encoding both TRPV1 and substance P is blocked, neither of these molecules are replaced, thus, both smooth muscle contractions, which are increased by substance P, and the excitability of the bladder, in which TRPV1 is involved are reduced. It should be noted, however, that the neurotoxic effect of capsaicin may develop within minutes and degenerating structures may disappear within 24 h (Hiura and Ishizuka, 1994; Jancsó, 1978; Jancsó et al., 1984).

An apparent shortcoming of vanilloid application is the irritable effect of these drugs, though Cruz (2004), Cruz et al. (1997a,b) and Silva et al. (2000) have reported that intravesical instillation of resiniferatoxin produces significantly less burning pain than capsaicin. The irritable effect of vanilloids could be overcome by the introduction of preparations containing vanilloids and a local anesthetic with a controlled release sequence and/or the development of analogues with reduced irritancy. In addition, investigations into the mechanisms of nociceptive signalling via vanilloid receptors and endovanilloids (Di Marzo et al., 2002) point to novel perspectives in pain management through modulating the activity of TRPV1 either by competitive or non-competitive TRPV1 antagonists (Garcia-Martinez et al., 2002; Pomonis et al., 2003). A common feature of the recently developed novel TRPV1 antagonists is that they attenuate both neuropathic and inflammatory pain. The data demonstrating the high potency and oral bioavailability of some of these compounds indicate that these antagonists are not only promising experimental tools but may bear significant therapeutic potentials in pain management (Pomonis et al., 2003).

The novel discoveries on the involvement of TRPV1 in pathological processes other than pain suggest that these new drugs might also be useful in the treatment of various diseases. However, as discussed above, the capsaicin receptor and capsaicin-sensitive neurons and non-neuronal cells might to be involved in physiological functions, such as the maintenance of tissue integrity. Thus, inhibition of

TRPV1 or desensitisation/degeneration of capsaicin-sensitive fibres, in addition of the beneficial effects may also produce loss of physiological functions.

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