REVIEW

Transient Receptor Potential Vanilloid 1 in animal tissues: An overview to highlight similarities and differences with human species

Cristina Vercelli [1], Raffaella Barbero [2], Giovanni Re [1]

[1]*Department of Veterinary Sciences, University of Turin, Largo P. Braccini 2, Grugliasco, Turin 10095, Italy*
[2]*Section of Serology and Animal Welfare, Istituto Zooprofilattico Sperimentale Piemonte Liguria Valle d'Aosta, Via Bologna 148, Turin 10095, Italy*

Correspondence: Cristina Vercelli
E-mail: cristina.vercelli@unito.it
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The purpose of this review is to give an overview of the identification and the characterization of Transient Receptor Potential Vanilloid 1 (TRPV1) in animal tissues. TRPV1 is a receptor belonging to the superfamily of Transient Receptor potential (TRP) and it was first identified in dorsal root ganglion in 1997. After, the scientific interest on this receptor increased, and nowadays it is possible to read a huge bibliography dealing with this receptor that is considered ubiquitarian. Actually, it was identified in the majority of animal and human tissues in physiological and pathological conditions. The involvement of TRPV1 receptor is considered as a key to understand aetiopathogenic mechanisms and to try to find a therapeutic treatment. In spite of the deep knowledge on TRPV1 molecular structure, more studies are required to better understand the cascade following its activation. For all the previous mentioned reasons, TRPV1 was investigated in species of interest of Veterinary Medicine and some of them are important animal models for human medicine, especially for oncology and analgesic therapeutic strategies.

Keywords: TRPV1; Comparative medicine; Veterinary Medicine; identification; pain; oncology

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Introduction

Transient receptor potential vanilloid 1 (TRPV1) is a non-selective cation channel belonging to the superfamily of Transient Receptor Potential (TRP) (Fig.1). TRPV1 is composed by six transmembrane domains with a pore region between the fifth and the sixth segment (S5-S6). This structure (Fig.2) was confirmed by electron microscopy and forms a tetrameric structure with a central localized pore [1]. Both its C- and N- termini are located intracellularly and it was demonstrated that they are involved in the regulation of the channel activity [2]. The first demonstration of the presence of TRPV1 was performed by Caterina and colleagues [3]: this receptor was cloned in dorsal root ganglion (DRG) cells and the identification was performed using capsaicin, the active compound of hot chilli peppers. The capsaicin molecule has a vanilloid moiety and for this reason these receptors are interchangeably referred to as capsaicin or vanilloid receptors (VRs) [4].

As cited previously, TRPV1 is a non-selective cation channel with a high permeability to Ca^{2+} and that can exhibit macroscopic outward rectification [3]. TRPV1 activation induces the depolarization of sensory nerve endings, and consequently could evoke a sequence of potentials from the spinal cord to the brain [4]. Electrophysiological and genetic

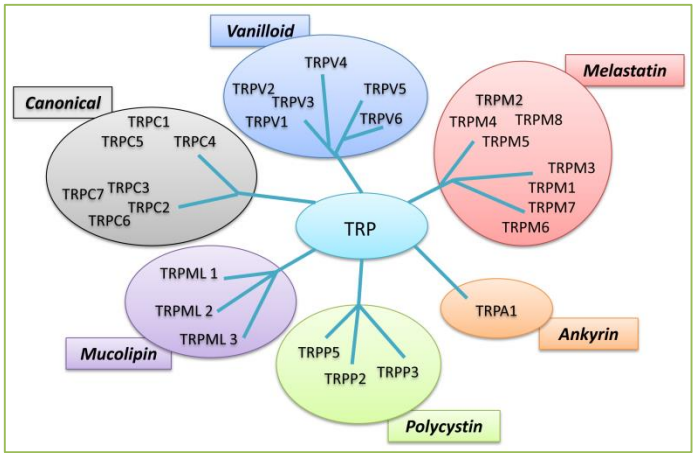

Figure 1. Representation of Transient Receptor Potential superfamily. Transient Receptor Potential superfamily could be divided into different subfamiliyes: TRPV (vanilloid), TRPML (mucolipin), TRPC (canonical) TRPA (ankyrin), TRPM (melastatin) and TRPP (polycystin).

studies demonstrated that TRPV1 is also activated by heat (>43°C) and that is involved in noxious thermal stimuli detection by primary sensory neurons [5,6]. Moreover, TRPV1 is sensitized by chemical substances produced during inflammation, i.e. extracellular protons and lipid metabolites that directly interact with the channel and can potentiate the effects of capsaicin or heat [5,7,8] (Fig.3).

TRPV1 of different species have been compared and evolutionary differences among vertebrates have been demonstrated by Saito and Shingai[9]. Especially in mammalians and birds, TRPV1 orthologues have been cloned, and their channel properties have been characterized in considerable details [10,11,12,13,14,15].

One of the most important differences exists with respect to sensitivity to capsaicin: rabbits and chickens are less sensitive to it than other vertebrates [11,14].

Saito and Shingai[9] identified four copies of mammalian thermo TRP homologs in chickens, nine in western clawed frogs, two in zebrafishes, and three in puffer fishes. The amino acid sequences of these TRPVs were aligned with those available in the databases and phylogenetic trees were reconstructed, using conserved portion containing ankyrin (ANK) repeat, transmembrane (TM), pore loop (PL), and TRP domains. According to the resulting findings, vertebrates' TRPVs were divided into four major clusters: TRPV1/2, TRPV3, TRPV4, and TRPV5/6 [16]. Moreover, they can be distinguished in those that are responsive to capsaicin, i.e. human [10], rat [3], guinea pig [12], and mouse [13], and those that are not responsive for, i.e. rabbit [14]. The reason behind capsaicin sensitivity can be found in a single threonine residue at amino acid position ^{550} within the S3 to S4 region [14].

All the similarities and the differences mentioned should be considered for comparative medicine researches because they could significantly influence experimental hypothesis and, consequently, the results. The following paragraphs deal with the mostly used experimental animal models and the most important similarities and differences between humans and animals will be highlighted.

TRPV1 expression in animal species

Mouse

The identification of TRPV1 in mouse was performed cloning RNA isolated from mouse spinal cord, primers derived from TRPV1 orthologues, and partial murine sequences from GenBank (AC087118.4 7) [13]. Subsequently, TRPV receptors involvement in transducing thermal and inflammatory pain was investigated in mice lacking the TRPV1 gene: these animals demonstrated deficits in hyperalgesia induced by inflammation, but partly maintained sensitivity to noxious heat [4]. Other studies established that TRPV1 deficient mice do not display thermal hypersensitivity following tissue injury [17,18], substantiating the hypothesis that capsaicin receptor is a polymodal integrator of noxious chemical and physical stimuli *in vivo*[11,19] .

It was demonstrated that direct phosphorylation by phosphokinase C (PKC) could activate TRPV1 and other cell surface receptors such as the purinergic receptor P2Y1, bradykinin BK2 receptor or the nerve growth factor (NGF) receptor TrkA[13]. The murine model was widely used in the past to study the modulation of TRPV1 activation via phorbol 12-myristate 13 acetate (PMA) inducing PKC phosphorylation. The study of Correll *et al.* [13] suggested that PMA-induced phosphorylation could decrease the heat threshold TRPV1 activation from 42°C to 32°C that means that TRPV1 could also be activated in a range of physiological temperatures, and that PKC-mediated phosphorylation could activate TRPV1. In contrast to this findings, other authors suggested that PMA-induced activation of PKC could only minimally activate TRPV1 compared to capsaicin - evoked activation [20,21].

The same study of Correll and colleagues [13] established that agonists like capsazepine, 5-iodio-resiniferatoxin (5-I-RTX) and BCTC against mice TRPV1 (mTRPV1) could have similar effects to that induce in rat TRPV1 (rTRPV1), while displaying significant differences compared to human TRPV1 (hTRPV1).

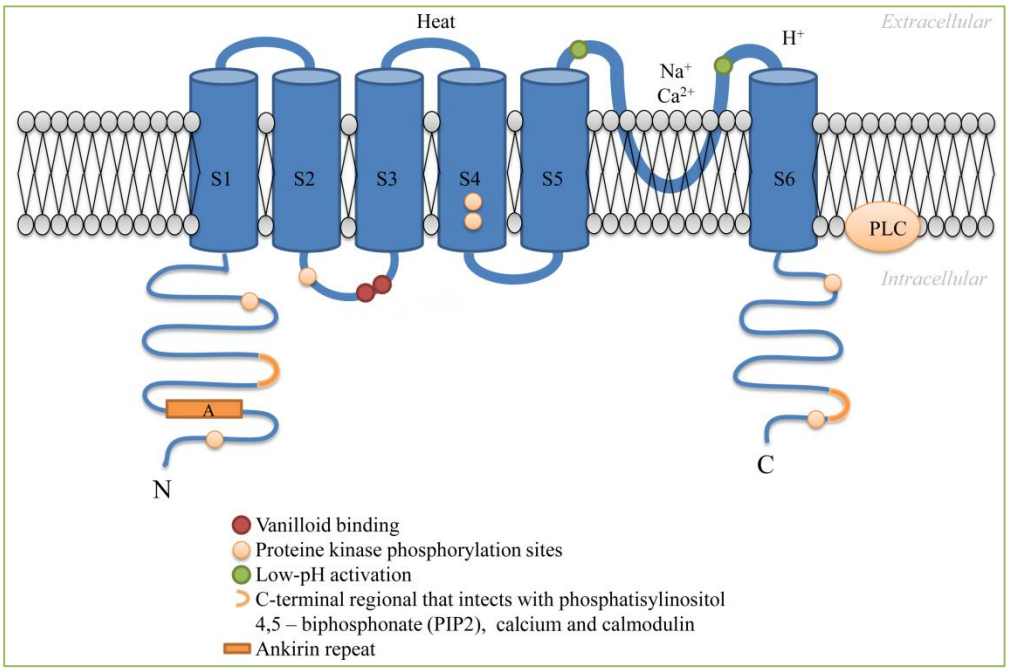

Figure 2. Molecular architecture of the vanilloid receptor. TRPVs are composed by six transmembrane segments (TM), a pore region between fifth and sixth segment, and cytoplasmatic N- and C-termini. These subunits constitute a tetramer around a central pore, responsible for the nonselective cation channel functions. The N-terminus can interact with cytosolic proteins, such as protein kinase A and C, Calcium/calmodulin-dependent protein kinase II. The cytosolic C-terminus domain carrying calmodulin (CaM) and phosphatydylinositol-4,5-bisphosphate (PIP2) binding sites.

Rats

TRPV1 was first identified in rat primary sensory neurons, and after it was recognized in different tissues and it was demonstrated is involvement in noxious thermal stimuli perception and propagation [3]. This result provided an important model system for the *in vitro* study of hyperalgesia and allowed to assume multiple implications of TRPV1 for comparative medicine researches.

Human TRPV1 and animal TRPV1s were compared and it was possible to calculate a grade of homology between hTRPV1 and rat (rTRPV1, 85.7%), guinea pig (gpTRPV1, 83.9%) and rabbit (oTRPV1, 87.8%) [13,14]. Nevertheless, responses to ligands could be extremely different considering the specific TRPV1: for instance, both human and guinea pig TRPV1s demonstrate little sensitivity to phorbol 12-phenylacetate 13- acetate 20-homovanillate (PPAHV) comparing to rTRPV1[13].

TRPV1 was also identified in rat trigeminal ganglion during a study that investigated the role of TRPV1 in orthodontic pain responses: results revealed that TRPV1 expression is modulated by experimental tooth movement and is involved in tooth-movement pain [22].

Rats were also used as experimental model for humans for bone pain. In the paper of Gui and colleagues [23], it was investigated the role of TRPV1 in bone pain following metastatic spread of breast cancer cells. TRPV1 positive neurons were more expressed in cancer-bearing rats and the substance P expression was not different, suggesting that TRPV1 responsive neurons were activated in the model [23]. Moreover, TRPV1 was identified in innervating femur in rat under physiological conditions and during osteoporosis it is possible to describe an increasing of TRPV1 expression [24].

Other studies were focused on identification and characterization of TRPV1 in airway smooth muscle cells and tracheal mucosa in rats. Yamamoto *et al.* [25] showed thatthe intraepithelial nerve endings and dense subepithelial network of nerve fibres were immunoreactive for TRPV1 in the epithelial layer. They investigate also TRPV2 receptor that was observed mainly innervefibres of the tracheal submucosal layer and in several intrinsic ganglion cells in the peritracheal plexus[25]. Double immunostaining revealed that some TRPV1-immunoreactive nerve fibres were also immunoreactive for substance P or calcitonin gene-related peptide, but neither neuropeptide co-localized with TRPV2 suggesting the possible involvement of TRPV1 in trachealnociception, and the different expression patterns ofTRPV1 and TRPV2 with neuropeptides may reflect different subpopulations of sensory neurons [25]. Zhao *et al.* [26]

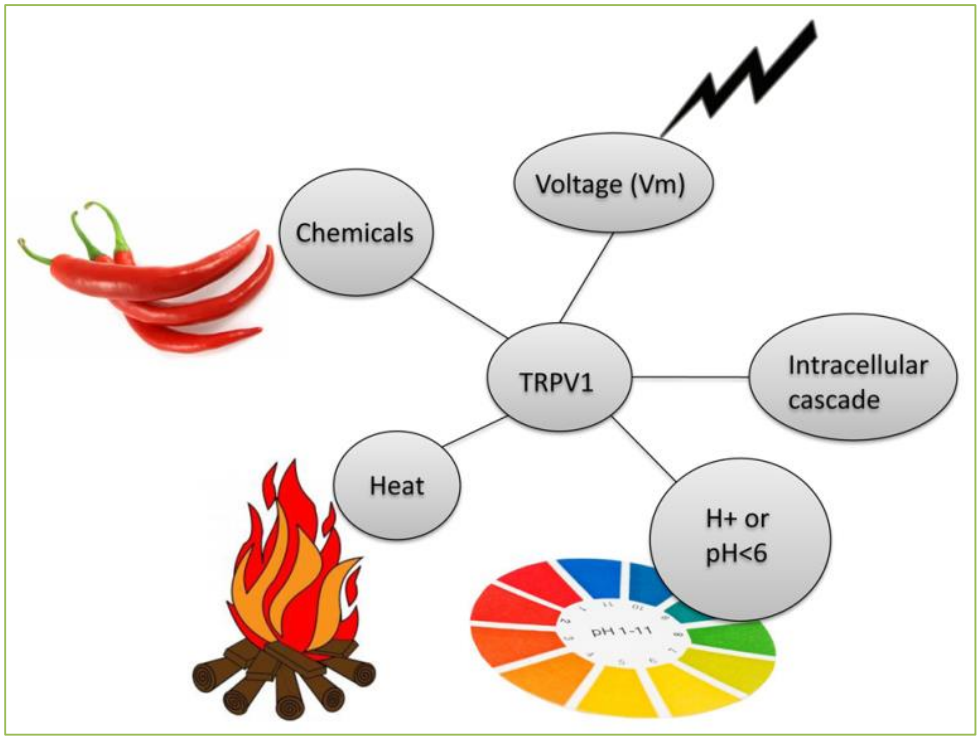

Figure 3.Multiple modes of TRPV1 activation. TRPV1 can be activated by a wide range of diverse chemical and physical stimuli. Chemical activation incorporates endogenous and exogenous agonists (many of them bind to the capsaicin side) and acidification (protonation of the receptor by H^+ binding). Physical stimuli include heat (threshold of 42-43°C) and membrane potential (depolarization causes channel opening). The activation of TRPV1 is described as "polymodal" or "multimodal" because different stimuli can contribute t ion channel activity.

demonstrated the expression and activity ofTRPV1 channel in proliferation of airway smooth muscle cells (ASMCs), one of the major contributors to airway remodelling and the basis of severe asthma. They highlighted that capsaicin inhibited apoptosis while capsazepine had the opposite effect. In human medicine, the study of McGarvey and colleagues [27] demonstrated that TRPV1 is overexpressed in patient with asthma and they hypothesised a therapeutic used of capsaicin to manage uncontrolled symptoms.

Amphibians

In amphibians, which are subject to thermal environmental variations (poikilothermal animals), the function of TRPV1 still remains unknown [16]. An early study reported that capsaicin did not affect substance P release from the spinal cord, although it changed nociceptive responses to cutaneous stimuli in *Rana esculenta*[28]. It was suggested by Kuffler and colleagues [29] that molecules of the heat sensor in the frog lack vanilloid sensitivity, as capsaicin does not produce any membrane current in *Rana pipiens* heat-sensitive DRG neurons. They demonstrated that frog DRG neurons can produce membrane current similar to that in mammalian primary sensory neurons after noxious heat application. Anyway, this current, and consequently the activation of the receptor, is not influenced by vanilloid ligands, while acids can inactivate it[29]. Szolcsányi[30]confirmed that frogs are completely insensitive to capsaicin (contrary to rTRPV1, where capsaicin easily induces noxious thermal stimuli) and temperature does not evoke any membrane current[3; 29]. These results suggested that TRPV1 in frogs probably lacks the domain for binding vanilloids and that probably this species should not be used as animal experimental model.

Rabbit

Identification and characterization of rabbit TRPV1 was performed by Gavva and colleague [14]. To assess this identification, a rat-rabbit (r/o) TRPV1 chimera was create after restriction cloning, hybridization and stable transfection. Binding and functional assays were performed and finally also electrophysiology tests were made.

This study demonstrate that cloned cDNA from a rabbit DRG appeared to be an orthologue of human TRPV1, primarily localized in sensory neurons, similar to both rat and human TRPV1. Binding assays using (^{3}H) resiniferatoxin (RTX) were performed and the results shown that oTRPV1 was relatively insensitive to vanilloid agonists, such as RTX, capsaicin, arvanil, and olvanil in comparison to rat and

human TRPV1. Authors tried to explain this phenomenon (that is analogous to the observations published by Jordt and Julius in 2002 concerning gpTRPV1) saying that a substitution in TM3 and TM4 regions (specifically on Ser^{505}-Thr^{550}) can occur from rat or human TRPV1 to oTRPV1, and this could modify its sensitivity to vanilloids. Anyway, even if Tyr^{511} is a conserved residue across species, probably it is not the only responsible for the differences in vanilloid sensitivity observed among oTRPV1 and other TRPV1s. Investigating the pharmacological differences among species, Gavva *et al*. [14] assessed that oTRPV1 can gain functional vanilloid sensitivity with a single residue substitution ($I^{550}T$) and with one additional residue change ($L^{547}M$), gaining also high affinity to (^3H)RTX. The same study highlighted that the reverse mutation cause the loss of vanilloid sensitivity and/or RTX binding for rat and human TRPV1[14].

Cat

TRPV1 was also identified in feline tissues, and considering the similarities with hTRPV1, this species was often used as animal model to study several human pathologies.

In 2005, Sculptoreanu and co-workers [31], investigated the role of TRPV1 receptor in interstitial cystitis (IC), a pathology that can affect feline and human urinary bladder. The investigator of this study used patch clamp techniques to examine primary afferent neurons during feline interstitial cystitis (FIC) and measuring TRPV1 responses to capsaicin in DRG neurons in normal and FIC affected cats. FIC neurons were increased in size and demonstrated a stronger capsaicin response that decreased slowly. Moreover, they demonstrated that phorbol 12,13-dibutyrate (PDBu), (a PKC activator) could reduce the desensitization of capsaicin responses in normal cat bladder and non-bladder neurons, but had no effect in FIC neurons. On the other hand, bisindolylmaleimide (PKC inhibitor), reversed the PDBu effects in normal cat neurons and normalized the desensitization of capsaicin responses in FIC neurons. Finally, they observed that that abnormalities in afferent neuron excitability may occur in DRG neurons innervating structures outside the pelvic cavity and this may explain the huge variety of symptoms of interstitial cystitis extend beyond the bladder, affecting other organs in the body.

The research group of Keay in 2014 [32], studied the role of urothelium in regulating bladder function during pathological conditions such as bladder pain syndrome/interstitial cystitis (BPS/IC), FIC and non-neurogenic idiopathic overactive bladder (OAB). All the mentioned pathologies are characterized by symptoms concerning lower urinary tract, such as urgency, incontinence, nocturia, and pain. Keay and co-workers[32]compared symptomatic and asymptomatic humans and cats, discovering that all symptomatic patients share some common features, including increased purinergic, TRPV1, and muscarinic signalling, increased urothelial permeability, and aberrant urothelial differentiation.

The study of Cheng *et al*.[33], identified the presence of TRPV1 in oesophageal mucosa in cats. Moreover, this study demonstrated the activation of TRPV1 by HCl and its enrolment in acid-induced inflammation and contraction of this organ. Capsaicin inhibits the contractions while 5-I-RTX had the opposite effect [33]. The results showed that TRPV1 HCl-induced activation in oesophageal mucosa induce the release of substance P and CGRP release from neurons and PAF release from epithelial cells [33].

A recent study [34] tried to demonstrate the role of TRPV1 in feline asthma. For this experiment, five cats were treated using Bermuda grass allergen (BGA) in order to induce asthma and 24 hours after this first sensitization, cats were treated with capsaicin. Unexpectedly and in contrast to the experimental hypothesis and to previously published data concerning asthma in other species, capsaicin did not result in concentration-dependent increases in airway resistance in a feline asthma model.

Dog

The first time that TRPV1 was identified in canine tissues was during the study of Phelps *et al*. [15]. Their project was addressed to clone dog TRPV1 cDNA from dog nodose ganglia, and to characterize this orthologue in transfected $HEK293^{OFF}$ cells. The dog orthologue showed the same structure and a strong homology to other mammalian TRPVs (89.3% to rabbit, 89.1% to human, 87.5% to rat, 85.2% to guinea pig, and 83.3% to mouse).

As explained previously, mammalian TRPV1 can be subdivided upon their functional response to capsaicin, based on the single threonine residue at amino acid position ^{550} in TM3 and TM4 regions. Dog TRPV1 contains a threonine residue at position ^{550}, suggesting a possible activation of the receptor by capsaicin. The primary amino acid sequence of dTRPV1 revealed the presence of a methionine at position ^{547}: the same site is responsible for PPAHV binding in rTRPV1[35, 36], and actually also dTRPV1 is responsive to PPAHV [15]. Phelps *et al*. [15] highlighted that the Hill slope value corresponding to resiniferatoxin was less than one, suggesting a negative cooperation of the dog receptor for this agonist. Moreover, dTRPV1 lacks serine at position, which is responsible for the sensitization of TRPV1 to PKA phosphorylation and to capsaicin: consequently, in dTRPV1,

these kind of activations might increase nociceptive perception [15]. The behaviour of dTRPV1 resulted the same of hTRPV1 and gpTRPV1 and opposite to rTRPV1 when exposed to BCTC and 5-I-RTX. Part of these findings was confirmed by Premkumar and Sikand[37]: capsazepine inhibits acid-induced activation of hTRPV1, but has no effects on the same activation in rTRPV1, but at the same time is able to inhibit heat-induced TRPV1 activation both in humans and rat.

The pharmacological features of dTRPV1 similar to human's orthologue, suggest that dog could be considered a good model for studying the role of TRPV1 in inflammatory diseases and nociception.

In 2013, TRPV1 expression in canine mammary adenocarcinoma cells, CF.41, was demonstrated [38]. In this study, the expression and functionality of dTRPV1 was investigated in a tumour cell line in comparison to human breast adenocarcinoma cell line (MCF-7 cells), where TRPV1 was first identified by Barbero *et al*. in 2006 [39]. Experiments on cell proliferation were done using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) technique and the results highlighted that all tested ligands (both agonists and antagonists) caused a significant decrease in MCF-7 cell proliferation. On the contrary, capsaicin and capsazepine were able to reduce significantly CF.41 cell proliferation. As cited previously, these results could depend on species-specific TRPV1 differences: capsaicin could activate rTRPV1 thanks to its binding with Arg^{114} and Glu^{761} residues [40]. To explain the different results obtained by vanilloid ligands on MCF-7 and CF.41 proliferation, it is possible that capsaicin and capsazepine might interact with TRP or non-TRP receptors. Hwang*et al*. [41] demonstrated that capsaicin act sinergically with 12-O-tetradecanoylphorbol-13-acetate (TPA) and can cause skin carcinogenesis, stimulating epidermal growth factor receptor. The cited study, used MTT proliferation assay that unfortunately is not useful to obtain information concerning the TRPV1 molecular mechanism underlying these responses, but the results seem to suggest that TRPV1-mediated effects in a canine model are not a good *in vitro* model for human breast adenocarcinoma.

Swine

Swine TRPV1 was recently investigated in the study of Hayes *et al*. [42] concerning the role of vagal nerve in the pulmonary neurobiology of acute lung injury. Authors explained that although differences exist between swine and human anatomy, the patterns of the vagal nerve are largely similar and closer in size than standard rodent models and for these reasons they tried to use swine as animal model to investigate human acute lung injury. In this study it was possible to demonstrate the presence of TRPV1 using immunofluorescence staining in nodose. Anyway, authors carefully aware that some species-specific changing can occur and that further studies are required.

Capsazepine: a (not always) TRPV1 antagonist.

One interesting finding of the study of Correll*et al*. [13] is that BCTC and 5-I-RTX function as potent antagonists across species against capsaicin, low pH-induced, and PKC mediated response. It was demonstrated that capsazepine cannot antagonize either acidic pH or PMA-induced mTRPV1 activation but can contrast a capsaicin-induced response. Differently, capsazepine completely blocks both a PMA-induced activation of hTRPV1 [20; 43], and a pH-induced activation of hTRPV1 [44] or gpTRPV1 [12]. mTRPV1 is pharmacologically more similar to rTRPV1, rather than hTRPV1 or gpTRPV1. Considering what previously mentioned, capsazepine can inhibit capsaicin-induced activation of TRPV1 but cannot block a pH-induced or PKC-mediated activation of TRPV1 in rodents, making this receptor different from other TRPV1 orthologues.

Moreover, capsazepine cannot reverse either carageenan-induced thermal hyperalgesia or in mechanical hyperalgesia in rat and mouse TRPV1, but can in guinea pigs [45]. The data of Correll *et al*. [13] are consistent with this argument and confirm that capsazepine is only able to inhibit a capsaicin-induced response for mTRPV1.

The activation of TRPV1 mediated by PKC should be inhibited to obtain an efficient antagonism of TRPV1 function *in vivo*, particularly under inflammatory conditions where activation of membrane receptors such as TrkA, P2Y1, or BK2 would lead to PKC-induced activation of TRPV1. The study of Gavva and colleagues [14] examining the importance of various conserved residues and identified the residue Leu^{547}, which appears to be essential for capsazepine antagonism after proton activation. Leucine is present in this position for human, guinea pig and rabbit TRPV1, while a methionine is present in that position for rat and for mouse TRPV1.

In rTRPV1, the residues $I^{514}M$, $V^{518}L$, and $M^{547}L$ allowed capsazepine to inhibit a pH-induced response for rTRPV1: functional assays confirm that these residues are involved in capsazepine interaction with different TRPV1 orthologues, and consequently can determine antagonist efficacy, particularly in regards to the various modalities of activation [36].

TRPV1 in comparative medicine

As mentioned at the beginning, during the last decades, several animal species were used as animal model for humans to investigate for possible therapeutic use of TRPV1, with a special attention to neuropatic and inflammatory pain and to oncology.

The paper of Trevisani *et al.* [46] deals with the ability of 5-I-RTX to inhibit cough induced by inhalation of capsaicin and citric acid in non- anaesthetized guinea pigs. 5-I-RTX is known to be an ultra-potent TRPV1 antagonist and in this study it was administered intraperitoneally or by aerosol before the stimulation with agonists. 5-I-RTX was able to reduce cough stimulation in a dose dependent manner. They proposed the therapeutic use of 5-I-RTX as antitussive drug. In must be underlie, that systemic administration of TRPV1 antagonists should be carefully considered because it could lead to the change of body temperature, gastrointestinal and cardiovascular functions. Furthermore, the blockade of TRPV1 has been shown to increase its own expression, thereby raising the possibility of rebound effects [37].

TRPV1 is expressed in C-fibre bladder afferents and also in urothelial cells from both rats [47] and humans [48]. Different investigators have studied the role of TRPV1 in OAB by using human urothelial tissues [32]. This pathology was separated into "sensory urgency" versus "detrusor overactivity" and in both situations it was observed an increasing TRPV1 mRNA expression, associated with sensory urgency, but not detrusor overactivity[49]. A study of Rios *et al.* [50] observed that treatment with resiniferatoxin (RTX), which blocks TRPV1, in not effective in patients with idiopathic detrusor overactivity and urgency incontinence (considered as idiopathic OAB). The trial of Apostolidis *et al.* [51] found a positive effect in patients with neurogenic OAB using a dose of 50nM of RTX. Taking into consideration these results, Keay *et al.* [32]concluded that the positive effects of RTX in OAB treatment are stronger in neurogenic patients (for instance, OAB post spinal cord injury) rather than in idiopathic OAB. Unfortunately all the mentioned studies could not complete clarify the role of TRPV1 in OAB because even if animal models are valuable tools to test perturbations in urothelial function, they not complete reflect the human pathology.

Some studies tried to understand if the level of expression of TRPV1 could be used as diagnostic or prognostic marker: some results highlighted that increased levels of TRPV1 are associated with a better prognosis of patients with hepatocellular carcinoma, whereas expression of TRPV1 is decreased in the urothelium of patients with advanced stage transitional cell carcinoma, [52]. In human breast cancer cells lines such as MCF-7, the overexpression of TRPV1 compared to normal gland can be considered a suitable prognostic marker [53]. Other studies showed that the receptor-mediated anti-tumour activity should be associated with induction of apoptosis following activation of TRPV1 and changes in cell calcium influx: calcium is involved in physiological cell processes and abnormal calcium functioning may occur during cancerogenesis[54]. Therefore, calcium channels could serve as anti-cancer therapeutic targets, because besides pro-apoptotic action, the activation of TRPV1 leads to anti-angiogenic, anti-migrative, anti-adhesive and anti-metastatic effects[55].

Oncologic researches demonstrated that TRPV1 is implicated not only in cell proliferation but also in pain modulation correlated to cancer, and several studies described the binding characteristics and clinical efficacy of selective TRPV1 agonists and antagonists [56]. TRPV1 mutations can lead to changes in TRPV1 responses to agonist stimulation: mutations at the sixth TRPV1 transmembrane domain can cause, for example, the reduction of ^{3}(H)RTX-binding affinity and mutations on pore domain significantly decrease the sensitivity to capsaicin [57]. The results of Vercelli *et al.* [38] of proliferation assays performed on MCF-7 cells confirmed the potential of TRPV1 agonists as anti-cancer drugs. These results found a confirmation in other studies that demonstrated that capsaicin could inhibit human cancer hormone-resistant cells and can provide chemopreventive effects [58]. Moreover, other studies demonstrated that capsaicin can mediate cell death of T24 (human bladder cancer), A172 (human glioma) [59; 60], and MCF-7 [61] cell lines, nevertheless the use of TRPV1 ligands in cancer treatment should always be careful, as explained previously.

Conclusions

The interest of the scientific community in TRPV1 increased significantly since this receptor has been identified in 1997. Looking at all the data available in literature, it seems clear that TRPV1 has a key role in modulation of inflammatory events, transmission and perception of pain, and recently it was demonstrated is enrolment in cancer aetiology and evolution. This interest was first address to human beings but nowadays it turns to Veterinary Medicine, looking for new therapeutic strategies. At the same time, discoveries concerning TRPV1 could be cross related in human or in veterinary medicine, always taking into consideration similarities and differences among species.

Conflict of interests

The authors declare that they have no conflicting interests.

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