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Transient Receptor Potential Vanilloid 1 Involvement in Animal Pain Perception

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Abstract: In last decades, Transient Receptor Potential Vanilloid 1 (TRPV1) has been the target of a large number of scientific investigations. It has been identified as a polymodal transducer molecule on a sub-set of primary sensory neurons which responds to various endogenous and exogenous stimuli including noxious heat (more than 42°C), protons and vanilloids such as capsaicin, the hot ingredient of chilli peppers. In mammals, TRPV1 displays a wide tissue and cellular expression including both the peripheral and central nervous system, with broad distribution and functions, in physiological and pathological conditions. Its primary localisation in sensory neurons reveals its key nodal point in pain transmission pathways. Nowadays, it is clear that TRPV1 is involved in inflammation, pain perception and thermoregulation in the majority of animals, including humans. Recently, a lot of studies tried to investigate some analgesic treatments applied on TRPV1. The aim of this review is to give to the readers a short overview of the TRPV1 involvement in pain perception and possible therapeutic applications, highlighting this topic in species of interest in veterinary medicine.

Keywords: TRPV1, Pain, Perception, Modulation, Animals

Introduction

All animals evolved a specific behaviour to prevent injury when exposed to physical and chemical stimuli (Kuffler *et al*., 2002). Vertebrates and invertebrates have an accurate and efficient perception of environmental stimuli in order to survive. Sensory neurons are able to detect these stimuli through receptors present in the peripheral nervous system and that can transduce information to the Central Nervous System (CNS). Among these, it is possible to find Transient Receptor Potential Vanilloid 1 (TRPV1), one of the most extensively studied member of the TRP family of ion channels (Montell, 2005).

TRPV1 is a non-selective cation channel that has a high permeability to Ca^{2+} and its activation induces sensory nerve endings depolarization and evokes a series of responses that propagates from the spinal cord to the brain (Premkumar *et al*., 2002; De Petrocellis and Moriello, 2013). It contributes to the detection of noxious thermal stimuli by primary sensory neurons of the pain pathway (Tominaga *et al*., 1998; Caterina and Julius, 2001). Electrophysiological and genetic studies demonstrated that TRPV1 is activated by heat (more than 42°C), acid pH, specific ligands (i.e.: Capsaicin) and by a number of chemical factors produced during inflammation (i.e., Diacyl-glycerol-DAG-, phosphatidylinositol 4,5-biphosphate-PIP2-, anandamide and other negatively charged lipids) that can directly potentiate the effects of capsaicin or heat (Tominaga *et al*., 1998; Jordt *et al*., 2000; Sprague *et al*., 2001; Lukacs *et al*., 2013; Senning *et al*., 2014).

TRPV1 was initially identified in small-diameter sensory neurons of dorsal root ganglia (Caterina *et al*., 1997) and subsequent studies shown that TRPV1 is also expressed in the cell bodies of small to medium sized primary afferents, located in dorsal root, trigeminal dorsal horn, nodose ganglia and in the brainstem nucleus tractus solitaries (Roberts and Connor, 2006). Moreover, different investigations cloned and characterised TRPV1 orthologues in the majority of mammalian and birds tissues (Hayes *et al*., 2000; Jordt and Julius, 2002; Savidge *et al*., 2002; Correll *et al*., 2004; Gavva *et al*., 2004; Phelps *et al*., 2005).

Science Publications

TRPV1 and Pain

TRPV1 activation in the primary afferent neurons results in the release of pro-inflammatory peptides and action potential-dependent with a release of glutamate from the peripheral nervous system and to a central widespread of neuropeptides, to amplify this signal and increase the sensitivity of the dorsal horn neurons to other incoming signals from the periphery (Roberts and Connor, 2006; Morales-Lázaro and Rosenbaum, 2014). It was demonstrated that TRPV1 has a double role: First, it is able to detect the damaging stimuli, perceived as painful and after it contributes to the transmission to the central nervous system (Roberts and Connor, 2006).

The perception of pain is not easily definable because it can vary for each species and subjects. Considering human beings, the definition of pain (as defined by the International Association for the Study of Pain-IASP-) is a physiological response to a noxious stimulus that causes an unpleasant feeling, decreasing the quality of life of those affected by it. Moreover, it should be borne in mind, that TRPV1 can be sensitized, leading to an increase in its response to a given stimulus or desensitized rendering it refractory to activation and could vary its expression (*down-regulation* or *up-regulation*) during tissue injury, inflammation and bone cancer (Ueda, 2006; Premkumar and Bishnoi, 2011; Pan *et al*., 2010).

This is why TRPV1 has become a promising target for pain-relieving therapies.

A persistent pain state could lead to hyperalgesia, which is defined as an increased and exaggerated responsiveness to a noxious stimulus. This can be due to a greater sensitization of the peripheral endings of nerve fibres or to alterations in TRPV1 gene/protein. In humans, it was demonstrated that hyperalgesia can occur in cancer, infection, post-operative pain and neuropathies associated with diabetes and Human Immunodeficiency Virus (HIV). Another aspect of neuropathic pain is allodynia, in which is pain is evoked by a normally innocuous stimulus and probably it is the last step of TRPV1 alteration in nociception (Roberts and Connor, 2006).

Many animal models were and are used to study TRPV1 in pain perception, transmission and alteration (hyperalgesia and allodynia), with the main goal to find an efficient treatment (Kuffler *et al*., 2002; Chen *et al*., 2009; Malek *et al*., 2012).

Frogs

TRPV1 was identified in frogs and its involvement was investigated in pain perception after a heat noxious stimulation (Ohkita *et al*., 2012). Noxious heat was applied to frog Dorsal Root Ganglion (DRG) neurons and consequently they produced a membrane current with similar properties to mammalian primary sensory neurons. Anyway this current was not influenced by capsaicin and its antagonists. A previous study shown that acids were able to induce a slow current membrane inactivation that was selectively carried by Na^+ and inhibited by noxious heat (Kuffler *et al*., 2002). Taking into consideration the results of both studies, it is possible to suppose that the TRPV1 reaction to noxious heat in frogs is different from that in mammals: TRPV1 plays the role of polymodal detector for noxious stimuli in mammals while in frogs these functions could be managed by distinct ion channels.

Mice

Mice were largely use to investigate TRPV1 in transducing thermal and inflammatory pain. Mice lacking the TRPV1 gene demonstrate deficits in thermal or inflammation pain, but maintain part of sensitivity to noxious heat (Premkumar *et al*., 2002). Moreover, TRPV1 deficient mice do not display thermal hypersensitivity following tissue injury (Caterina *et al*., 2000; Davis *et al*., 2000), substantiating the hypothesis that capsaicin receptor is a polymodal integrator of noxious chemical and physical stimuli *in vivo* (Jordt and Julius, 2002; Rehman *et al*., 2013). The murine model was also used in the recent past to study the modulation of TRPV1 activation via Phorbol 12-Myristate 13-Acetate (PMA) inducing Protein Kinase C (PKC) phosphorylation. Some studies suggested that PMA can induce phosphorylation of PKC modulating TRPV1 activation and leading to a decrease of the heat threshold of TRPV1 activation from 42°C to 32°C that means that TRPV1 could also be activated at physiological temperatures and PKC-mediated phosphorylation should be sufficient to activate TRPV1 (Correll *et al*., 2004). Others suggested that PMA-induced activation of PKC could only minimally activate TRPV1 (Crandall *et al*., 2002; Vellani *et al*., 2001) compared to capsaicin-evoked activation. The study of Correll *et al*. (2004) was in contrast with the previous one and found that PMA induced activation of TRPV1 is highly efficacious at the physiological temperature of 37°C and they were able to monitored and assessed the full induction of TRPV1 by a PKC-mediated pathway.

Rats

Rat is another widely used animal model to investigate how TRPV1 can act in nociception. This receptor was identified in trigeminal ganglion in a study concerning the role of TRPV1 in orthodontic pain responses: Results revealed that TRPV1 expression is modulated by experimental tooth movement and it is actively involved in tooth-movement pain (Qiao *et al*., 2014).

The paper of Gui *et al*. (2013) 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, but substance P (a neuropeptide involved in nociception) release has no difference, suggesting that TRPV1 responsive neurons were activated in the model. Moreover, TRPV1 was identified in innervating femur in rat under physiological conditions and during osteoporosis experimental model where it is possible to appreciate an increaseof TRPV1 expression (Yoshino *et al*., 2014).

The study of Yamamoto *et al*. (2007) identified and characterized TRPV1 in intraepithelial and subepitelial nerve ending in airway smooth muscle cells and tracheal mucosa in rats. They investigate also TRPV2 that was mainly observed in nerve fibres of the tracheal sub mucosal layer and in intrinsic ganglion cells in the peritracheal plexus (Yamamoto *et al*., 2007). TRPV1-immunoreactive nerve fibres were also positive for substance P or Calcitonin Gene-Related Peptide (CGRP-a peptide involved in transmission of pain sensation in both central and peripheral nervous system neurons), but neither neuropeptides were co-localized with TRPV2: These results suggested the possible involvement of TRPV1 in thacheal nociception, but the different expression ofTRPV1, TRPV2 and neuropeptides may reflect the presence of subpopulation of sensory neurons (Yamamoto *et al*., 2007). A recent study investigated the expression and the functionality of TRPV1 channel in Airway Smooth Muscle Cells (ASMCs) proliferation: This process is the basis of airway remodelling that can lead to severe asthma and the results of this study demonstrated that specific agonists and antagonists could modulate cell proliferation (Zhao *et al*., 2014).

Avians

In avian species, it was identified the cVR1 (chicken analog of TRPV1), that has functional properties similar to mammalian TRPV1 but shows residual sensitivity to vanilloid compounds, as evidenced at high capsaicin concentrations (Jordt and Julius, 2002). Differences between avian and mammalian TRPV1 orthologues could explain why mammalian predators are repelled by pepper plants, whereas birds are favoured as vectors for seed dispersal (Tewksbury *et al*., 1999; Tewksbury and Nabhan, 2001).

Dogs

The first identification of TRPV1 in dog Tissues (dTRPV1) was done by Phelps *et al*. (2005): The receptor displayed similarities to human’s orthologue suggesting that dog could be a good model for inflammatory diseases and nociception. Nowadays, canine experimental model concerning TRPV1 is commonly used in oncologic researches (Pihno *et al*., 2012; Vercelli *et al*., 2013).

Therapeutic Strategies using TRPV1 Agonists and Antagonists

Recent studies tried new pharmacological treatments specifically targeted to TRPV1 receptorfor the control of pain and inflammatory conditions in a variety of diseases and injury states, considering the development of several TRPV1 agonists and antagonists.

Clinical trials were performed on healthy or suffering of chronic pain volunteers: Local application of capsaicin (as 0.025%-0.075% cream preparations) resulted better than placebo at reducing pain associated with post-herpetic neuralgia, diabetic neuropathy, osteoarthritis and musculoskeletal disorders (Roberts and Connor, 2006; Chong *et al*., 2007; Kwak, 2012). Anyway it is important to underlie that the local application leads to a burning sensation and erythema, but few serious side effects (Spruce *et al*., 2003; Galluzzi *et al*., 2007; Brito *et al*., 2014). Capsaicin application also produces a release of substance P and CGRP in the skin and it is possible that continued application of capsaicin depletes peripheral terminals of these pro-nociceptive substances (Kwak, 2012). Finally, continuous or repetitive capsaicin application leads to a blunting of many cutaneous sensory modalities and this is associated with a reversible loss of epidermal nerve fibres coinciding with the onset of the sensory deficits (Kwak, 2012). High-dose capsaicin, when tolerated, has the potential for long-term analgesia in certain types of neuropathic pain (Smith and Brooks, 2014) and recently it was reviewed that TRPV1 is also involved in synaptic plasticity with functional implications of TRPV1 in CNS, partly due to its multimodal form of activation and highlighting the potential pharmacological implications of TRPV1 in the brain (De Petrocellis and Moriello, 2013; Edwards, 2014).

The ultrapotent TRPV1 agonist, Reniferatoxin (RTX) is studied because it seems that it can lead to a long term TRPV1 desensitisation, lasting for weeks (Choi *et al*., 2009). RTX has been used in the treatment of urinary incontinence in humans (Bley, 2004) and for cancer bone pain (Brown *et al*., 2005).

Several TRPV1 antagonists have been studied to alleviate or reverse mechanical and thermal hyperalgesia associated with inflammatory pain. The main hypothesis concerning their mechanism of action is that antagonists could block TRPV1 activation through interfering with conformational changes required for channel activation at distinct sites from those for protons or capsaicin actions, such as the putative camphor activation site (Roberts and Connor, 2006; Morales-Lázaro and Rosembaum, 2014). The first reported TRPV1 antagonist, capsazepine, was discovered by modifying the chemical backbone of capsaicin (Walpole *et al*., 1994). Capsazepine competes for the capsaicin-binding site on TRPV1, blocks capsaicin-induced channel activation in neonatal rat dorsal root ganglion (Brito *et al*., 2014).

Some study tried to use TRPV1 antagonists in the reduction of mechanical hyperalgesia and in models of inflammatory and post-operative pain with positive effects, but the mechanism of action is not yet perfectly clear. Capsazepine was found to be extremely useful in laboratory research, leading to the hypothesis that it could be considered an important candidate for clinical use.

Unfortunately, clinical trials belied this chance. One of the reasons is that capsazepine has a low metabolic stability and poor pharmacokinetic properties as demonstrated in rodents (Vriens *et al*., 2009). Moreover, it is apparently non-selective (Broad *et al*., 2008; Pal *et al*., 2009; Wong *et al*., 2009) and appearing or cross-reactive: While inhibiting TRPV1, capsazepine also inhibited nicotinic acetylcholine receptors voltage-gated Ca^{2+} channels and TRPM8 (Liu *et al*., 1997; Weil *et al*., 2005). Capsazepine illustrated species-dependent effects in various models of chronic inflammatory and neuropathic pain possibly due to the species-related differences in the binding of capsazepine to TRPV1: Anti-hyperalgesic effect of capsazepine was more effective in reversing the persistent inflammatory and neuropathic pain in guinea pig than in mice or rats (Walker *et al*., 2003).

The 5-Iodo-Renifertoxin (5-I-RTX) was administered in systemically to attenuate bone cancer related pain (Ghilardi *et al*., 2005).

It is necessary to remark that the systemic use of TRPV1 antagonist should be carefully considered because, it must be borne in mind that TRPV1 channel is expressed also in physiological conditions and that it was demonstrated that a systemic TRPV1 block can occur (Premkumar and Sikand, 2008).

Conclusion

Since its cloning over a decade ago, research on TRPV1 has grown considerably and nowadays TRPV1 is one of the most studies TRP receptors. The increasing interest on TRPV1 is not only the role of this channel in mediating inflammatory and chronic pain (Re *et al*., 2007), but also is involvement in a huge number of pathologies (especially oncology) and diseases ranging from diabetes and urinary incontinence to arthritis and hearing loss (Bley, 2004; Brito *et al*., 2014). However, although the compounds used in clinical trials, the therapeutic utility of TRPV1 agonist and antagonists is yet to be validated unequivocally, both for humans and animals.

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Author’s Contributions

All authors equally contributed to write this manuscript.

Ethics

This review is original and was not published elsewhere. The corresponding author confirms that all authors have read and approved the manuscript.

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