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Review

Vanilloid Receptors – Comparison of Structure and Functions in Mammals and Invertebrates

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The vanilliod receptor subfamily belongs to the transient receptor potential family of ion channels. Vanilloid receptors are calcium-permeable channels highly expressed in many different cells, both excitable and nonexcitable, in invertebrates (nematodes, insects) and vertebrates (mammals). These receptors are sensitive to a wide range of stimuli (chemical, mechanical, osmotic and temperature) that often activate the same channel. This review focuses on recent information, both bibliographic and experimental evidence of the author, concerning the structure and functions of vanilloid receptors, especially those connected with thermoregulation.

Key words: Transient receptor potential family, vanilloid receptors, capsaicin, mammals, insects.

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Vanilloid receptors belong to a large family of receptors termed the transient receptor potential family (TRP family). The first member of the transient receptor potential family was discovered in the fruit fly (*Drosophila melanogaster*), as a receptor that takes part in phototransduction processes (COSENS & MANNING 1969; MONTELL *et al*. 2002). As in mammals, photoreceptor cells of the fruit fly respond to light with long-lasting and continuous receptor potentials (HUANG 2004). One group of *Drosophila* mutants was discovered in which the photoreceptor's response to light was transitory and disappeared quickly. These mutants were called *trp* – transient receptor potential mutants (HARDIE 2007). Further research revealed that the *trp* gene, responsible for mutation, encodes a cation channel permeable to calcium ions (MINKE & COOK 2002). Recent work has uncovered many channels that show sequence and structural similarities to the fruit fly TRP channel. All are classified in a single transient receptor potential family (HUANG 2004). Members of this superfamily are involved in many sensory processes, for example, vision and hearing in invertebrates, and pain, temperature and gustatory sensation in mammals. Many of these receptors take part in osmosensation or in the regulation of the intracellular calcium concentration (NIEMEYER 2005). Presently the TRP ion channel family is divided into 7 subfamilies: TRPC (canonical), TRPV (vanilloid), TRPM (melastatin), TRPP (polycystins), TRPML (mucolipins), TRPA (ANTKM) and TRPN (NOMPC). The TRPN subfamily is found only in invertebrates. The TRP superfamily is formed only on the grounds of amino acid sequence similarities and basic channel structure (PADINJAT & ANDREWS 2004; RAMSEY *et al*. 2006). The mode of action and selectivity of channels in particular subfamilies differ. Some can be activated by ligands, others are activated by physical stimuli (for example temperature or mechanical stimuli) (GAUDET 2008). All members of the transient receptor potential superfamily are non-selective cation channels with various selectivity ratios for particular cations, for example permeability to calcium ions versus sodium ions can amount from >100:1 to even <0.05:1 (HUANG 2004). TRP channels have 6 transmembrane segments with cytoplasmic terminals C (COOH) and N (NH_2). This structure is typical for many different channels, among others also for voltage-gated channels. Transient receptor potential channels show structural similarities mainly within transmembrane segments, however, sequence identities in these segments may reach only 20% (CLAPHAM *et al*. 2003).

Vanilloid receptors

One of the best known transient receptor potential subfamilies is the vanilloid receptor (TRPV) subfamily. Its name is connected with the chemical substance that activates the first discovered channel of this subfamily. This substance is capsaicin, a chemical compound belonging to the vanilloids, responsible for the spicy taste of pepper. Similarly to other TRP family members, vanilloid receptors have 6 transmembrane segments (S1-S6) and N and C cytoplazmatic tails. A short hydrophobic segment between the fifth and sixth domain takes part in the formation of the channel pore. The relatively long N-terminus has three to four ankyrin repeats (FERRER-MONTIEL *et al*. 2004). Ankyrin repeats are sequence motifs composed of 33 amino acids involved in protein-protein interactions (XIANGSHU *et al*. 2006). Transmembrane segments of the channel create subunits which presumably gather in order to form homo- or heterotetrameric complexes (HELLWIG *et al*. 2005). Assembly of four subunits is essential for forming a functional channel (NIEMEYER 2005). Vanilliod receptors function as non-selective cation channels with differing calcium ion permeabilities (O'NEIL & BROWN 2003).

Vanilloid receptors in mammals

Six vanilloid receptors have been discovered in mammals. The first of these, vanilloid receptor subtype 1 – TRPV1, was discovered in 1997 (CATERINA *et al*. 1997). This receptor is highly expressed in dorsal root ganglia and trigeminal ganglia and to a lesser degree in the central nervous system (in hypothalamus), liver, kidney and other organs (O'NEIL & BROWN 2003). Vanilloid receptor subtype 1 is a cation channel with higher selectivity for divalent cations ($Ca^{2+} > Mg^{2+} > Na^{+} \approx K^{+} \approx Cs^{+}$), and shows a relatively higher permeability ratio to calcium ions than sodium ions (P_{Ca}/P_{Na}=9.60; P_{Mg}/P_{Na}=4.99) (CATERINA *et al*. 1997). This receptor is sensitive to a wide range of stimuli. It can be activated by various chemical substances as well as many physical stimuli. TRPV1 opens in response to capsaicin and other vanilloids by direct binding of these chemical compounds to an intracellular binding site on the channel (O'NEIL & BROWN 2003). Moreover, lipid molecules such as anandamide – an amide derivative of arachidonic acid, can be agonists of the channel (CATERINA 2007). Vanilloid receptor subtype 1 is also activated by allicin from garlic (MACPHERSON *et al*. 2005), piperine from black pepper (MCNAMARA *et al*. 2005), resiniferatoxin (SZALLASI & BLUMBERG 1999), ethanol (TREVISANI *et al*. 2002) and camphor (XU *et al*. 2005).

Physical stimuli activating the channel include protons (low pH) and high temperature >42°C. The mechanism of activation by temperature is not very well known. It is assumed that TRP channels may show a weak dependence on membrane potential, and temperature is able to shift this voltage dependence towards physiological membrane potentials which in consequence results in receptor stimulation (NILIUS *et al*. 2005). Protons (pH<5.9) open the channel by binding extracellularly near the channel pore at two sites: E600 and E648 (JORDT *et al*. 2000). Agonist binding causes the opening of the channel which results in ion, mainly calcium, influx and cell membrane depolarization. This generates an action potential which is propagated in the nervous system. TRPV1 activation is perceived as pain and heat (SZALLASI & BLUMBERG 1999).

Other vanilloid receptors found in mammals are also temperature sensitive. Vanilloid receptor subtype 2 is activated by temperature above 53°C (PATAPOUTIAN 2005) and also mechanical and osmotical stimuli (MURAKI *et al*. 2003). Neither capsaicin nor low pH stimulate the channel (BENDER *et al*. 2005). TRPV2 is highly expressed in sensory neurons (WOODBURY *et al*. 2004). Vanilloid receptor subtype 3, similar to TRPV2, is stimulated by heat (temperature >33°C) and does not respond to stimuli which activate TRPV1, i.e. capsaicin and protons (SAITO & SHINGAI 2006). TRPV3 is expressed in dorsal root ganglia, trigeminal ganglia and skin cells as well (O'NEIL & BROWN 2003). Another vanilloid receptor that reacts to temperature is TRPV4. As other members of this subfamily, vanilliod receptor subtype 4 is a nonselective cation channel, expressed in many different cells, both excitable and nonexcitable (among others: skin, tracheal epithelium, kidneys, salivary and sweat glands or mechanosensory cochlear hair cells). This channel participates in temperature sensation (in the range of 28-34°C), mechanosensation and osmoregulation (opens due to extracellular hipotonicity) (SIDHAYE *et al*. 2006).

The most distant members of this subfamily in mammals are vanilloid receptors subtypes 5 and 6. These channels are expressed mainly in the small intestine and kidney epithelia and reveal many features that differentiate them from other TRPs. TRPV5 and TRPV6 are highly selective calcium channels, they conduct calcium ions over 100 times better than sodium ions. The key site for such high-affinity binding of calcium ions is probably the residue of aspartic acid in position number 542. The channels are constantly active at physiological membrane potentials; they become inactive when the intracellular calcium concentration rises, presumably due to processes involving calmodulin. It was also shown that a decrease in extracellu-

lar pH leads to the closing of the channels. These receptors are responsible for the active influx of calcium ions from kidneys (TRPV5) and intestine lumen (TRPV6) to blood (VAN DE GRAAF *et al*. 2006).

Modulation of vanilloid receptor functioning

Vanilloid receptor functioning in mammals is modulated by phosphorylation. These modifications may lead to major changes in channel properties.

Vanilloid receptors are regulated by protein kinases. Phosphorylation of TRPV by protein kinase C enhances the channel's sensitivity to protons, ligands (including capsaicin) and temperature (LEE *et al*. 2005). The precise sites of phosphorylation by PKC are Ser-502 and Ser-800 (YAO *et al*. 2005). Also phosphorylation of the channel on Ser-116 and Thr-370 potentiates its response to heat and capsaicin. This process can also lead to the reduction of desensitization of the channel (see below) (HU *et al*. 2002; YAO *et al*. 2005). JUNG *et al*. (2004) demonstrated that $Ca2^{+}$ – calmodulin dependent kinase II (CaMKII) phoshorylates vanilloid receptor subtype 1. This process precedes channel activation by capsaicin and is essential for receptor stimulation. Additionally, phosphorylation induced by NGF (nerve growth factor) on a tyrosine residue (Y200) of the vanilloid receptor by Src kinase is important for surface expression of the receptor (ZHANG *et al*. 2005). Vanilloid receptor subtype 2 is also modulated by PKA which phosphorylates the channel and sensitises it to heat. PKC phosphorylates TRPV4 and increases its sensibility as well (YAO *et al*. 2005).

The opposite process to sensitization is desensitization of the receptors. Repeated or prolonged activation of TRPV channels leads to desensitization and receptor insensivity to different stimuli. For example, desensitization of TRPV1 can be caused by multiple administration of capsaicin. Capsaicin-desensitized animals become insensitive to high ambient temperatures. Since they do not feel heat, they do not activate thermoregulatory mechanisms that protect them from overheating (for example, behavioural escape from hot places, physiological evaporation or cutaneous vasolidation) (Fig. 1) (TĘGOWSKA *et al.* 2008). Desensitization is irreversible even months after capsaicin administration (JANSCÓ-GÁBOR *et al*. 1970). The physiological role of desensitization is in need of explanation, but it may be an adaptation of the peripheral nervous system to perceiving pain. That is why capsaicin is a potential analgesic (GAVVA *et al*. 2007). TRPV1 desensitization appears to depend on Ca^{2+} and is connected with channel dephosphorylation by calcineurin (NUMAZAKI *et al*. 2003; MOHAPATRA & NAU 2003). Calcineurin is an enzymatic protein with phosphatase activity. In cells, it forms a complex with calcium and calmodulin and causes activation of phosphatase, which dephosphorylates the channel (HOGAN & LI 2005).

Vanilloid receptors in insects

Vanilloid receptors have also been discovered in insects. So far only two TRPVs were found in the fruit fly, *Drosophila melanogaster*. These include Nanchung (CG5842), a channel composed of 833 amino acids, and Inactive (CG4536), a receptor composed of 1123 amino acids. Nanchung was named after a fruit fly mutant which was deaf ('nanchung' means 'deaf' in Korean). On the other hand mutants deprived of Inactive demonstrated defects in locomotion and mating anomalies. NAN and IAV have the same structure as vanilloid receptors in mammals, although they possess five ankyrin repeats in the N-tail (TRPV1 has only 3 ankyrin repeats) and they are also cation channels with higher permeability to calcium ions. Nanchung and Inactive are activated by osmotic stimuli, but surprisingly they do not react to capsaicin, menthol nor temperature (from 10°C to 60°C), i.e. stimuli that activate other members of the transient receptor potential family. Both receptors are expressed only in chordotonal neurons, at the same site in cilia. The antennal chordotonal organ in flies is a hearing organ. NAN and IAV form one complex and are interdependent of each other.

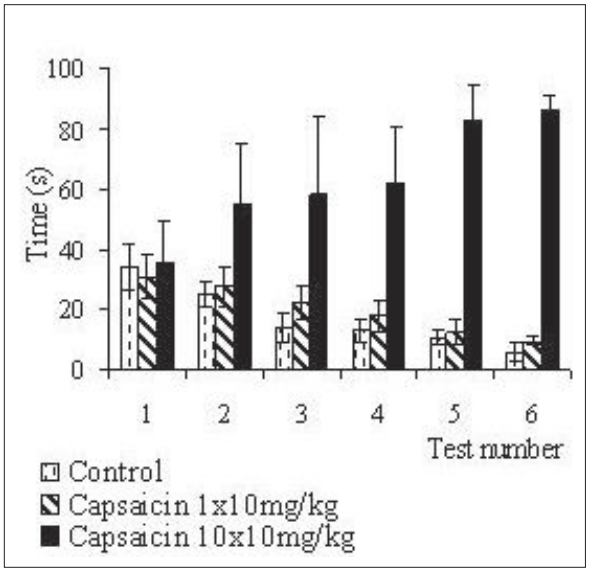

Fig. 1. Desensitization to capsaicin in mice. Capsaicin exerts an influence on time (mean± SD) of staying on a heated plate (50°C). Control mice, as well as mice after one injection reacted similarly – in each successive test (1-6) they needed less time to escape from the heat plate. Mice after ten injections spent much more time on the heat plate with every next test. This suggest that these animals became capsaicin and heat-desensitized (after TĘGOWSKA *et al.* 2008).

They both are required for auditory transduction, so *Drosophila* mutants deprived even of only one of these receptors are deaf. The mechanism of channel activation is not clear. It appears that these channels are mechanoreceptors that open due to cilia movement (LIEDTKE & KIM 2005; GONG *et al*. 2004).

To date only these two TRPV have been discovered in insects. Researchers have found 13 members of TRP family in the fruit fly, including members of TRPC subfamily (TRP, TRPL and TRPγ) and TRPN subfamily (NOMPC) (JÖRS *et al*. 2006; COREY 2003). Studies on this issue are of great interest but so far little information on vanilloid receptors in insects is available. Worth mentioning is that capsaicin exerts an influence on the American cockroach, *Periplaneta americana*. Application of this vanilloid caused hyperthermia, manifested in selection of higher ambient temperatures in a thermal gradient in comparison to the control group (ADAMKIEWICZ *et al*. 2008). Surprisingly, vanilloid receptors have not been discovered in this insect, although capsaicin has an influence on them. The effect of the action of capsaicin suggests the existence of vanilloid receptors. A similar situation occurred during the discovery of opioid receptors. In the 1950s it was postulated that analgesia induced by morphine may be connected with action on a specific receptor. This postulate was based mainly on strict stereospecifity of the analgesic properties of morphine. A final proof that analgesic function of morphine is related to action on an opioid receptor was presented after breeding a μ-opioid receptor knockout mouse (SIMON *et a*l. 1973; CORBETT *et al*. 2006). The effect of capsaicin observed in insects can be the basis for an intensified search for vanilloid receptors in insects.

TRPV in other invertebrates

Vanilloid receptors are also found in the nematode *Caenorhabditis elegans*. The first of these, OSM-9, was discovered in 1997 (COLBERT *et al*. 1997). *C. elegans* mutants deprived of this channel did not respond to very high and noxious osmotic concentrations, did not respond to mechanical stimuli and demonstrated deficiencies in response to odorants (LIEDTKE 2006). The OSM-9 channel is expressed in amphid sensory neurons. Amphids are the major chemosensory organs of free living nematode species. They are localized mainly in front of the worm's body and contain 12 pairs of sensory neurons, ten of which express vanilloid receptor OSM-9 (TOBIN *et al*. 2002; KAPLAN & HORVITZ 1993). Subsequently, four more TRPV in *C. elegans* were reported: OCR-1, OCR-2, OCR-3 and OCR-4. Their names stem from the first letters of the phrase 'OSM-9 and capsaicin receptor related channels' (O'NEIL & BROWN 2003). Of all members of the nematode receptor subfamily, only OSM-9 is closely related to mammalian TRPV – it shows 27% identity with TRPV1 and 26% identity with TRPV4. The OCR channels are more similar to each other (30%-40% identity) than to OSM-9 (20%-25% identity) and they are distant to vanilliod receptors in mammals (TOBIN *et al*. 2002; O'NEIL & BROWN 2003). Similarly to *Drosophila*, in *C. elegans* two channels (OSM-9 and OCR-2) co-operate with each other as well. Their localization and stability in amphids are interdependent, so it has been suggested that they form a heteromultimeric channel. This complex formation is fundamental for sensory functions, including mechanosensation, osmosensation and olfaction (MONTELL 2003). The functions of other vanilloid receptors in the nematode are unknown.

OSM-9 and OCR-2 functioning can be regulated by polyunsaturated fatty acids, i.e. a subset of 20-carbon PUFAs could be involved in olfactory and nociceptive behaviors (KAHN-KIRBY *et al*. 2004). It is assumed that repellents stimulate metabotropic receptors, which activate Gi-like proteins. These proteins cause lipid mobilization from phospholipids containing polyunsaturated fatty acids and their release leads to vanilloid receptor activation. *C. elegans* TRPV can be stimulated directly by mechanical, chemical or osmotic stimuli (BARGMANN 2006).

Vanilloid receptors are found both in vertebrates and invertebrates. They show structural and functional similarities in mammals as well as in insects and nematodes, especially noticeable after capsaicin administration. Our experiments revealed that both mammals and insects demonstrate a similar response to capsaicin injections. Application of capsaicin to the American cockroach (*Periplaneta americana)* placed in a thermal gradient of linear temperature in the range of 10°C to 45°C, caused an increase in the preferred temperature in comparison to the control group (Fig. 2) (ADAMKIEWICZ *et al*. 2008). A similar behaviour was observed in mice (TĘGOWSKA *et al*. 2008). Mice placed in a thermal gradient after capsaicin injection preferred higher temperatures than control animals (except for several hours of the second day of the experiment during which they chose lower temperatures than control mice). Fig. 3 presents differences in mean preferred temperatures in the temperature gradient between control animals and animals after capsaicin application (both mice and cockroaches). The differences between cockroach and mouse behaviour may stem from homeothermy in mice. These animals can use both behavioural and physiological thermoregulatory mechanisms,

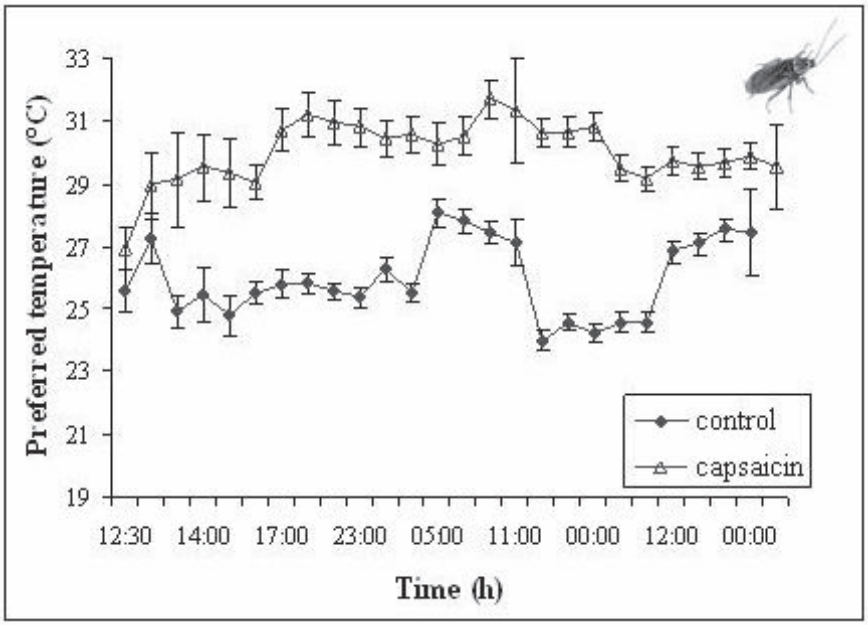

Fig. 2. Changes in behavioural thermoregulation in *Periplaneta americana* after application of 10μl of 10^{-3}M capsaicin solution. Capsaicin caused a significant ($P<0.05$) increase in preferred temperature (after ADAMKIEWICZ *et al*. 2008).

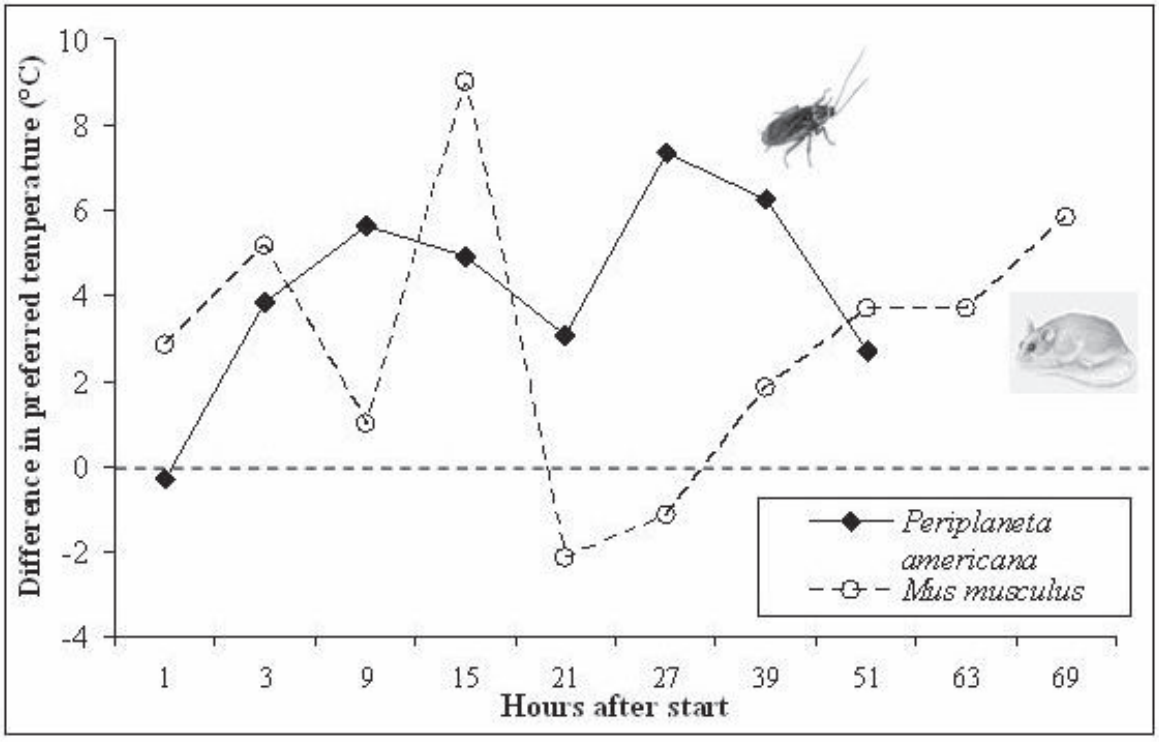

Fig. 3. Differences in mean preferred temperatures (°C) in a thermal gradient between control and animals after capsaicin application. Application of capsaicin on cockroaches (10 μl from 10^{-3}M capsaicin solution) caused hyperthermia (intoxicated insects chose higher temperatures than control animals in the thermal gradient – the difference in preferred temperatures is positive). Mice after injection of capsaicin (10 mg/kg) in the first 20 hours of the experiment preferred higher temperatures than control animals, then they moved to cooler places. Starting from hour 36, mice after capsaicin injection chose higher temperatures than control individuals (after ADAMKIEWICZ *et al*. 2008; TĘGOWSKA *et al*. 2008).

whereas changes in functioning of thermoreceptors in insects may have an influence only on their behavioural thermoregulation.

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