British Journal of Pharmacology (2008) 155, 1142–1144

0007–1188/08 $32.00
www.brjpharmacol.org

COMMENTARY

Hot target on nociceptors: perspectives, caveats and unique features

J Szolcsányi

Department of Pharmacology and Pharmacotherapy, Faculty of Medicine, University of Pécs, Pécs, Hungary

Identification of C-polymodal nociceptors and the selective action of capsaicin on them by acting on a putative receptor, which has been cloned 11 years ago, initiated a burst of interest in pharmacology of nociceptors. Capsaicin receptor transient receptor potential vanilloid-1 (TRPV1) being a noxious heat-gated cation channel gated also by several exogenous and endogenous substances serves as a nocisensor to generate graded receptor potentials in these sense organs. Impressive data on pathways involved in sensitization/desensitization of the channel revealed in isolated cells should also validate at the level of nerve endings and lipid raft around TRPV1 could modify the channel gating. Capsaicin-sensitive nociceptors subserve dual sensory-efferent functions: tachykinins and calcitonin gene-related peptide released from them elicit local tissue responses as neurogenic inflammation and release of somatostatin evokes systemic anti-inflammatory and antihyperalgesic effects. TRPV1 gene-deleted mice show subtle changes in physiological regulations, therefore TRPV1 is a promising but challenging target for drug research.
British Journal of Pharmacology (2008) **155,** 1142–1144; doi:10.1038/bjp.2008.374; published online 10 November 2008

Keywords: capsaicin; sensory-efferent function; C-polymodal nociceptor; resiniferatoxin; somatostatin; lipid raft; TRPV1 cation channel; thermosensor; nocisensor; sensocrine

Abbreviation: TRPV1, transient receptor potential vanilloid-1

The idea of the existence of nociceptors that respond to various 'noxious' stimuli was first predicted by Sherrington 102 years ago. Unequivocal evidence for this hypothesis was revealed by Bessou and Perl (1969), describing the largest subset of C-afferent fibres that have sense organs excited by heating to a noxious level, elevated mechanical stimuli and also to acid or other irritant chemicals. These sense organs were termed 'polymodal nociceptors' or 'polymodal receptors' (Perl, 1996). From a pharmacological point of view, it seemed to be a promising task to discover compounds that selectively inhibit the function of nociceptors. Nevertheless, as so often happens, not a rational approach, but serendipity, had become the starting point. Analysing the chemoanalgesia elicited by high dose of capsaicin—discovered and first mentioned by Nicholas Jancsó during the 1940s of the last century—I published evidence during the 1970s that capsaicin excites and desensitizes the C-polymodal nociceptors by acting on a putative 'capsaicin receptor' and that its action is highly temperature dependent (Szolcsányi, 1996). It had become clear that capsaicin-type agents have highly selective action on this major nociceptive group of primary afferent neurons, preoptic warm detectors and some groups of chemosensory interoceptors, but not on mechanoreceptors or efferent neurons of the autonomic nervous system. Thus, this 'chemoceptive' afferent system has been classified as 'capsaicin-sensitive' for differentiation among nerve-mediated responses referring to a receptor-mediated action that elicits dual stimulatory and lasting blocking effects. Attempts to relate capsaicin sensitivity and its neuroselective action to neuropeptides depleted by capsaicin was a kind of misinterpretation of the original proposal and led, in some cases, to misleading conclusions. Ablation of sensory neurons in rats after neonatal treatment turned out to be not restricted to nociceptor population, but indiscriminate loss of C-afferents occurs owing to marked secondary changes (Szolcsányi, 1996, 2002). On the other hand, the concept about the existence of the 'capsaicin receptor' has been proven and led to cloning the first temperature-gated ion channel now named as the transient receptor potential vanilloid-1 (TRPV1). Gating TRPV1 by noxious hot stimuli and its sensitization by endogenous inflammatory mediators, such as bradykinin or prostaglandin, or directly gating by lipoxygenase metabolites or protons formed an impressive body of evidence for its integrative 'nocisensor' function. Transfected cell lines expressing this nocireceptive transdu-

Correspondence: Professor J Szolcsányi, Department of Pharmacology and Pharmacotherapy, Faculty of Medicine, University of Pécs, H-7624 Pécs, Szigeti u. 12., Hungary.
E-mail: janos.szolcsanyi@aok.pte.hu
Received 9 September 2008; accepted 20 September 2008; published online 10 November 2008

cer molecule has opened promising new perspectives for high-throughput screening in drug research.

Transient receptor potential vanilloid-1 does not fit to the classical grouping of ion channels as voltage-gated vs ligand-gated ones. Beyond the thermosensor character, its function is to signal endogenous or exogenous chemonociceptive stimuli either from the outer or inner side of the channel. From this point of view, its ligand-gated opening is extremely promiscuous unlike the classical ligand-gated ones. Regarding the voltage-gated nature discussed in the review (Holzer, 2008), increasing the temperature or the effect of capsaicin results in enhanced proportion of open channels as a function of voltage, but single-channel open probability elicited by resiniferatoxin is not voltage dependent (Raisinghani *et al*. 2005), and highly hyperpolarized TRPV1-transfected yeast cells were robustly activated by noxious heat or capsaicin (Myers *et al*. 2008). These unique features of the gating characteristics may be related to the physiological function of TRPV1, being one of the key ion channels that generates graded receptor potential at the nociceptive endings to reach a critical level of depolarization for propagation action potentials triggered by true voltage-gated ion channels.

The membrane topology and domain structure of TRPV1 on Figure 1 is different from that depicted in earlier reviews, as crystal structure identification of the cytosolic N chain of the channel has recently revealed six instead of the predicted three ankyrin repeats (Lishko *et al*. 2007). ATP binding to these domains sensitizes the channel opening, providing the first example of binding a small molecule to ankyrin repeats. The C-terminal cytosolic chain by binding the scaffolding protein A kinase anchoring peptide 79/150 has a pivotal function for channel sensitization and to induce in this way hyperalgesia evoked by bradykinin or prostaglandin E_2 (Zhang *et al*. 2008). The possible function of lipid raft around the ion channel was deduced from structure activity/affinity relationships of two 'vanilloid' agonists as capsaicin and resiniferatoxin (Szolcsányi, 2002). Without going into details, published data in this line clearly showed, for example, that omitting or replacing the 4–OH substitution at the vanilloid moiety of capsaicin completely abolished its effect, whereas in the case of the 'ultrapotent' resiniferatoxin, elimination this H-bonding substitution diminished only slightly its affinity and potency, which were mainly determined by the keto substitution at the hydrophobic diterpene skeleton. Thus, it is not surprising that replacement of resiniferatoxin-H[3] by capsaicin in binding studies resulted in false prediction of different receptors for these agonists. Instead, it has been proposed that the two agonists open the same TRPV1 channel at partly allosteric binding sites, and hydrophobic bonds to membrane structures around the ion channel also have a significant modulatory function in channel gating (Szolcsányi, 2002). Our recent *in vitro* studies by depleting cholesterol with methyl-β-cyclodextrin seems to support this conclusion, particularly at the level of nerve endings.

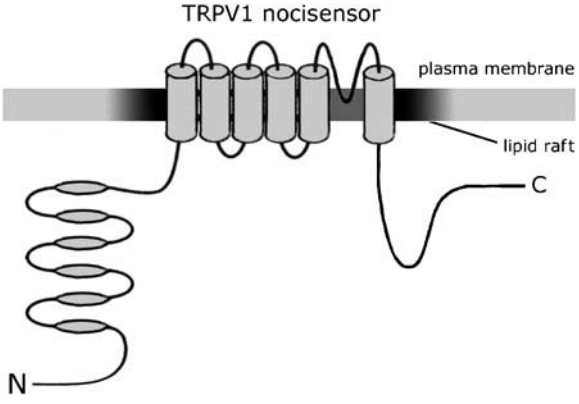

Figure 1 Predicted domain structure of TRPV1 in the plasma membrane.

It is important to emphasize that TRPV1 is a nocisensor and that its gating function has a dedicated significance at the nerve endings. Differences between intracellular membrane structures in cell bodies and nerve endings underline the importance to validate at this level the fascinating molecular interactions revealed already in isolated cells. TRPV1 expression in some neurons of the brain or non-neural cells seems to be at least 30-fold lower than that in sensory neurons (Caterina, 2007). Further *in vivo* studies are needed to determine their functional significance and their operational features, for example, in the case of preoptic thermosensors.

Unique feature of TRPV1-expressing subset of primary afferent neurons is that their peripheral endings subserve a dual sensory-efferent function. In contrast to the classical axon reflex theory, it is coupled at the level of the same nerve endings (Szolcsányi, 1996). As TRPV1 is a cation channel influx of both Na^+ and Ca^{++}, well explained this dual function. Tachykinins and calcitonin gene-related peptides mediate most of the local tissue responses, such as neurogenic inflammation. An unexpected observation in the rat—that is, antidromic stimulation of the cut peripheral end of dorsal roots elicited pronounced systemic anti-inflammtory effect—resulted in the discovery that somatostatin released from a subset of capsaicin-sensitive endings reaches the circulation and elicits systemic anti-inflammatory and antihyperalgesic effects. TRPV1-expressing nerve terminals stimulated at a low frequency of 0.1 Hz—the firing rate of polymodal nociceptive afferents that is not painful in humans—elicit cutaneous hyperaemia and systemic 'sensocrine' anti-inflammatory effects (Szolcsányi *et al*. 1998, 2004).

Although multiple functions of sensory neurons supplied by TRPV1 and the existence of various further TRPV1-expressing cells might interfere with its nocisensor function, the fact that TRPV1 gene-deleted mice show no evidence for serious impairment in physiological regulations, behaviour and lifespan indicates that the development of TRPV1 antagonists is still a promising but challenging task.

Acknowledgements

This work was supported by Hungarian Grants: OTKA T-049027 and RET-008/2005.

References

Bessou P, Perl ER (1969). Response of cutaneous sensory units with unmyelinated fibers to noxious stimuli. *J Neurophysiol* **32**: 1025–1043.

Caterina MJ (2007). Transient receptor potential ion channels as participants in thermosensation and thermoregulation. *Am J Physiol Regul Integr Comp Physiol* **292**: R64–R76.

Holzer P (2008). The pharmacological challenge to tame the transient receptor potential vanilloid-1 (TRPV1) nocisensor. *Br J Pharmacol* **155**: 1145–1162 (this issue).

Lishko PV, Procko E, Jin X, Phelps ChB, Gaudet R (2007). The ankyrin repeats of TRPV1 bind multiple ligand and modulate channel sensitivity. *Neuron* **54**: 905–918.

Myers BR, Bohlen ChJ, Julius D (2008). A yeast genetic screen reveals a critical role for the pore helix domain in TRP channel gating. *Neuron* **58**: 362–373.

Perl ER (1996). Cutaneous polymodal receptors: characteristics and plasticity. *Progr Brain Res* **113**: 21–37.

Raisinghani M, Pabbidi RM, Premkumar LS (2005). Activation of transient receptor potential vanilloid 1 (TRPV1) by resiniferatoxin. *J Physiol* **567**: 771–786.

Szolcsányi J (1996). Capsaicin-sensitive sensory nerve terminals with local and systemic efferent functions: facts and scopes of an unorthodox neuroregulatory mechanism. *Progr Brain Res* **113**: 343–359.

Szolcsányi J (2002). Capsaicin receptors as target molecules on nociceptors for development of novel analgesic agents. In: Kéri Gy, Toth J (eds). *Molecular Pathomechanisms and New Trends in Drug Research*. Taylor and Francis: London, pp. 319–333.

Szolcsányi J, Pintér E, Helyes ZS, Oroszi G, Németh J (1998). Systemic anti-inflammatory effect induced by counter-irritation through a local release of somatostatin from nociceptors. *Br J Pharmacol* **125**: 916–922.

Szolcsányi J, Pintér E, Helyes ZS (2004). Sensocrine function of capsaicin-sensitive nociceptors mediated by somatostatin regulates against inflammation and hyperalgesia. In: Handwerker HO, Brune K (eds). *Hyperalgesia: Molecular Mechanisms and Clinical Implications*. IASP Press: Seattle, pp 113–128.

Zhang X, Li L, McNaughton PA (2008). Proinflammatory mediators modulate the heat-activated ion channel TRPV1 via the scaffolding protein AKAP79/150. *Neuron* **59**: 450–461.