British Journal of Pharmacology (2008) 155, 1139–1141

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

COMMENTARY

Activation of the transient receptor potential vanilloid-1 (TRPV1) channel opens the gate for pain relief

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Pharmacological modulation of the transient receptor potential vanilloid-1 (TRPV1) receptor function offers a promising means of producing pain relief at the level of the primary sensory neuron. In this issue of the *BJP*, the pharmacological approaches and the available experimental data that focus on the TRPV1 receptor to achieve therapeutically useful alleviation of pain and inflammation are reviewed. The potentials to inactivate TRPV1 receptor function by site- and modality-specific TRPV1 antagonists, uncompetitive TRPV1 blockers and drugs interfering with TRPV1 sensitization, are evaluated. A crucial issue of producing pain relief at the level of the nocisensor remains whether it can be achieved solely through inactivation of the TRPV1 receptor or TRPV1 agonist-induced defunctionalization of the whole primary afferent neuron is required. The accumulated evidence indicates that both pharmacological modulation of the intracellular trafficking of the TRPV1 receptor and defunctionalization of the nocisensors by TRPV1 agonists are promising novel approaches to tame the TRPV1 receptor.
British Journal of Pharmacology (2008) **155,** 1139–1141; doi:10.1038/bjp.2008.375; published online 10 November 2008

Keywords: capsaicin; vanilloid; TRPV1; pain; analgesia; lipid raft; neurodegeneration; neuropeptides

Abbreviations: NGF, nerve growth factor; TRPV1, transient receptor potential vanilloid-1

Pharmacological modulation of the nociceptor function remains a promising way of producing analgesia at the level of the primary sensory neuron. A continuously increasing body of experimental evidence demonstrates that the transient receptor potential vanilloid-1 (TRPV1) receptor is a central molecular integrator of a variety of noxious stimuli and has a central function in the transmission of nociceptive information. In this issue of the *BJP*, Holzer (2008) critically reviews the pharmacological approaches and the available experimental data that focus on the TRPV1 receptor to achieve therapeutically useful alleviation of pain and inflammation. Pharmacological perturbation of the function of this channel was envisaged as a promising approach through which to produce pain relief in clinical settings (see for reviews, Nagy *et al*., 2004; Holzer, 2008; Knotkova *et al*., 2008). In view of the multitude of membrane receptors sensitive to noxious stimulation and expressed in the primary nociceptor, it was probably not entirely unexpected that in TRPV1 knockout animals inflammatory heat hyperalgesia was significantly reduced, but noxious heat sensation was not definitely affected. Thermal and mechanical sensitization were not inhibited either in a murine model of neuropathic pain (see for reviews, Nagy *et al*., 2004; Holzer, 2008; Knotkova *et al*., 2008). Recent experimental and clinical findings also cast doubt on the therapeutic effectiveness and value of TRPV1 antagonists in relieving pain (Holzer, 2008; Knotkova *et al*., 2008). However, capsaicin and other vanilloid agonists of TRPV1 have proved to be very efficient in producing long-lasting antinociception and analgesia in rodents, monkey and humans (Nagy *et al*., 2004; Knotkova *et al*., 2008). This apparent paradox may be explained by earlier findings on the dose (concentration)-dependent effects of capsaicin on nociceptor afferent fibres. The sensitivity of the TRPV1 receptor, as assessed by the potency of an agonist ligand to induce ionic currents or generate action potentials, is greatly reduced or abolished after repeated administration of capsaicin at very low (nanomolar) concentrations, a phenomenon termed pharmacological desensitization (Winter *et al*., 1995). However, the marked antinociceptive actions of capsaicin administered by various routes, including systemic, perineural, intrathecal, intracisternal or topical applications may not be accounted for by this mechanism and may not be attributed solely to modulation of the functions of the receptor itself (Nagy *et al*., 2004). A significant antinociceptive effect is brought about only by the administration of capsaicin at higher concentrations/doses that produce functional capsaicin desensitization ('defunctionalization') characterized by reduction/loss of responsiveness to a variety of

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Received 20 October 2008; accepted 20 October 2008; published online 10 November 2008

other physical and chemical algogenic stimuli (Winter *et al*., 1995; Nagy *et al*., 2004; Holzer, 2008; Knotkova *et al*., 2008). The possible mechanisms and phases of functional capsaicin desensitization are still unclear. The reduced sensitivity to noxious stimulation ensues rapidly after the administration of capsaicin; as an example, the chemical pain sensitivity of the cornea is abolished almost immediately after the administration of capsaicin either topically, systemically or intracisternally, and is independent of the peptide levels in the affected sensory ganglion neurons (Winter *et al*., 1995; Nagy *et al*., 2004). The rapid onset and the long duration of the antinociceptive effect of vanilloids have led to the suggestion that the analgesic (and anti-inflammatory) effects of capsaicin may be accounted for by a rapid degeneration/destruction of sensory ganglion cell axons and/or peripheral and central axon terminals (Jancsó *et al*., 1977; Jancsó, 1992; Simone *et al*., 1998; Dux *et al*., 1999; Nagy *et al*., 2004). Indeed, experimental data from independent laboratories support the notion that the antinociceptive effects of capsaicin administered through different routes are associated with degenerative changes within the different domains of the nociceptive primary sensory neuron and the consequent loss of peripheral or central nociceptor-specific macromolecules and receptors (see for reviews, Jancsó, 1992; Knotkova *et al*., 2008). The degenerative phenomena may be confined to the immediate site of application of vanilloids, but they may affect distant parts of the primary sensory neuron, resulting in transganglionic changes in the spinal dorsal horn. Moreover, peripheral application of capsaicin or resiniferatoxin may result in a substantial, though not complete loss of C-fibre afferents in the peripheral nerves (Jancsó, 1992; Dux *et al*., 1999). These changes have been suggested to provide the morphological substrates of the long-lasting antinociceptive action of capsaicin both in animals and humans (Simone *et al*., 1998; Dux *et al*., 1999; Nagy *et al*., 2004). Indeed, in the rat and also in humans, the antinociceptive effect of capsaicin and the recovery of function were paralleled by the loss and regeneration of cutaneous axons (Simone *et al*., 1998; Nagy *et al*., 2004; Knotkova *et al*., 2008).

The mechanism of fibre loss after perineural capsaicin treatment is still unclear. It appears that a slow dying-back-type delayed degeneration process may be involved, which is related to the inhibition of the retrograde transport of trophic agents, such as nerve growth factor (NGF; Jancsó, 1992; Dux *et al*., 1999; Nagy *et al*., 2004). Inhibition of axonal transport processes and the consequent decreased availability of trophic factors may also be implicated in the defunctionalization of the remaining sensory C-fibres, as the maintenance of the nociceptive properties of at least some afferent fibres is critically dependent on NGF, even in the adult animal (Winter *et al*., 1995).

Some salient features of the effects of capsaicin and related vanilloids cannot be explained by direct action on the TRPV1 receptor. The local regulatory, sensory efferent functions of capsaicin-sensitive primary afferents are mediated by neuropeptides released from nociceptor nerve endings (Holzer, 2008). The mechanisms of long-term depletion of such sensory neuropeptides as substance P and calcitonin gene-related peptide, which may also serve as transmitter molecules in nociceptive primary afferent neurons, are unclear, but may not be directly coupled to receptorial action. Inhibition of peptide synthesis on account of a reduced retrograde intraneuronal transport of NGF and possibly other neurotrophins may be implicated (Jancsó, 1992; Knotkova *et al*., 2008). Indeed, blockade or inhibition of the axonal transport of sensory neuropeptides, NGF, specific proteins of sensory ganglion neurons (TRPV1, thiamine monophosphatase) and exogenous tracer molecules has been demonstrated (Jancsó, 1992; Sántha and Jancsó, 2003). The blockade of axoplasmic transport induced by capsaicin is highly selective: motor and sympathetic efferent fibres are not affected similarly to capsaicin-insensitive afferents, thereby providing an approach to the separation and classification of functionally different subgroups of C-fibre afferents. The intriguing possibility that endogenous vanilloids may have similar effects on axoplasmic transport and the regulation of neuronal peptide levels has not yet been explored. It is conceivable, however, that the release of endogenous vanilloid agents acting on the axons or pre-terminal portions of nociceptor fibres may modulate the chemistry and, in turn, the function of nociceptive afferents. The observation that an endogenous vanilloid, *N*-oleyldopamine, induced hyperalgesia in a rat model of inflammatory pain lends support to this assumption (Chu *et al*., 2003).

Recent findings suggest that new facets of the TRPV1 function seem to be emerging (Holzer, 2008). Assuming that the TRPV1 receptors may be associated with lipid rafts to facilitate interaction with specific lipid metabolites that activate the receptor, Liu *et al*. (2006) showed that the depletion of cholesterol from cultured primary sensory ganglion cells reduced capsaicin-activated currents. Further, morphological studies demonstrating a phenotypic switch of capsaicin-sensitive primary afferent neurons after traumatic or chemical injury resulting in the altered expression of GM1 ganglioside, an integral component of membrane lipid rafts, led to the hypothesis that pharmacological perturbation of the ganglioside metabolism may affect neuronal capsaicin sensitivity, and in turn, the nociceptive function (Sántha and Jancsó, 2003). The findings demonstrated that inhibition of the key enzyme of neuronal ganglioside synthesis, glucosylceramide synthase, resulted in a marked reduction of capsaicin sensitivity and also decreased TRPV1 immunoreactivity in cultured sensory ganglion cells (Jancsó *et al*., 2008). The confinement of TRPV1 to lipid rafts is of importance for the activation, membrane trafficking and interactions with other signalling complexes also localized in membrane lipid microdomains. The pharmacological perturbations of cellular cholesterol and/or ganglioside synthesis that interfere with the lipid raft function may represent a novel therapeutic modality that allows the modulation of TRPV1 function and pain sensation.

Acknowledgements

This study was supported in part by grants from the Hungarian National Science Foundation (OTKA 63663 and PD 73259) and ETT 193/2006. PS was supported by the János Bolyai research scholarship.

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