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# COMMENTARY

## NEUROPHARMACOLOGICAL MECHANISMS OF CAPSAICIN AND RELATED SUBSTANCES

ANDY DRAY*
Sandoz Institute for Medical Research, London WC1E 6BN, U.K.

Capsaicin is an important molecule (Fig. 1) because of its highly selective effects of unmyelinated C- and poorly myelinated Aδ-mammalian primary sensory neurons, particularly warm thermoceptors and polymodal nociceptors [1–5]. Capsaicin-sensitive neurons exhibit several important features. During inflammation, their responsiveness to exogenous stimuli changes such that some neurons become hypersensitive to physiological stimuli, while others, normally quiescent and unresponsive, now become responsive to external stimulation and behave as nociceptors [1]. In humans, local applications of capsaicin to the skin or mucous membranes produce a transient burning pain and hyperalgesia [5, 6] by activation and sensitization of primary afferent C- and probably Aδ-neurons. Capsaicin also induces a longer lasting secondary hyperalgesia (an increase in sensitivity some distance away from the injected site). This phenomenon, however, is now thought to be due to an increase in neuronal excitability in the spinal cord [7]. Paradoxically, however, capsaicin can also produce an inactivation of nociceptive afferent fibres, and it is this property which may be exploited to produce future analgesic drugs.

Capsaicin-sensitive neurons release glutamate and a number of neuropeptides such as substance P, neurokinin A, somatostatin, and calcitonin gene-related peptide (CGRP)† as central neurotransmitters of nociceptive signals. These transmitter substances are also involved in producing long-term alterations of spinal excitability, associated with increased spinal reflex activity. These mechanisms may be involved in the development of secondary hyperalgesia, as mentioned earlier, and perhaps in the production of neuropathic pain processes such as allodynia whereby stimulation of low threshold afferent Aβ-fibres can be perceived as a noxious stimulus [7, 8]. Capsaicin-sensitive afferent fibres are also able to change their responsiveness to exogenous stimuli, particularly following the pathophysiological effects of inflammatory mediators (e.g. kinins, prostanoids). Indeed, afferent C-fibres are capable of releasing neuropeptides (substance P, CGRP) at their peripheral endings. Once released these peptides exert a number of effects. They stimulate secretions (gastrointestinal, salivary), contract smooth muscle, dilate microvessels and increase microvascular permeability allowing the leakage of plasma proteins from venules [2, 3]. This latter effect, and the neuropeptide-induced mast cell degranulation, are related to the pathophysiological mechanisms of neurogenic inflammation.

Presently there is a good deal of debate on the physiological classification of capsaicin-sensitive neurons. It is clear that this type of neuron exhibits afferent (nociceptor) activity as well as efferent properties but it is unclear how to classify neurons that become responsive to physiological stimuli only under the influence of inflammatory products or exogenous irritants. Indeed capsaicin-sensitive neurons appear to encompass the properties of "multifunctional neurons". This topic, however, requires a discussion which is outside the scope of

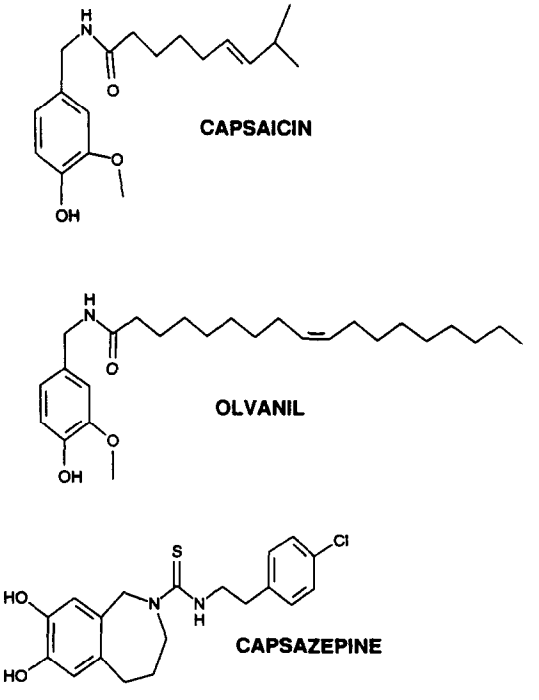


Fig. 1. Structures of capsaicin and the analgesic/anti-inflammatory analogue, olvanil. The third structure shown is the selective, competitive capsaicin antagonist, capsazepine.

* Correspondence: Dr. Andy Dray, Sandoz Institute for Medical Research, 5 Gower Place, London WC1E 6BN, U.K. Tel. (071) 387–4445; FAX (071) 387–4116.

† Abbreviations: CGRP, calcitonin gene-related peptide; and NGF, nerve growth factor.

the present commentary. In this article the properties of capsaicin will be reviewed with the aim of explaining the various neuropharmacological and functional changes that it produces.

*The capsaicin receptor and ion channel*

Detailed studies of capsaicin-induced activation of nociceptive neurons have been made using cultured sensory neurons and fibres *in vitro* [9, 10]. These studies have shown that capsaicin induces a depolarization, during which there is an increase in membrane permeability to cations, particularly to calcium and sodium ions [9, 11, 12]. The capsaicin-induced accumulation of calcium or the flux of rubidium and guanidinium ions has been exploited to quantify the effects of capsaicin-like molecules [9].

Capsaicin-induced activation of sensory neurons is likely to be produced by an interaction with a specific membrane receptor. Evidence for a capsaicin receptor has been provided from earlier studies using a variety of capsaicin derivatives [13–15] and a capsaicin-like photoaffinity probe [16]. Identification of a capsaicin binding site, using radiolabeled capsaicin, has not been successful. However, specific, saturable, capsaicin displaceable binding has been shown using the ultrapotent capsaicin analogue resiniferatoxin as a binding ligand [17]. This naturally occurring irritant activates sensory neurons and nociceptors in a manner identical to that of capsaicin [18, 19]. In addition, systemically administered resiniferatoxin shows potent antinociceptive and anti-inflammatory activity [18, 20]. More recently, evidence confirming the existence of a capsaicin receptor, localized to mammalian sensory neurons, has been obtained using a novel competitive antagonist, capsazepine (Fig. 1). Capsazepine has been shown to be a highly selective antagonist of capsaicin-induced activation of nociceptors both *in vitro* and *in vivo* [21, 22].

The existence of a capsaicin receptor has suggested that there may be an endogenous ligand for it. A possible candidate has been low pH. This view was supported by the striking similarity between the activation of C-neurons by capsaicin and that produced by low pH [23]. However, it is unlikely that the effect of pH is susceptible to the selective capsaicin antagonist capsazepine. Further studies have revealed specific capsaicin binding proteins on sensory neurons but a capsaicin antiserum was unable to detect endogenous capsaicin-like activity in normal or inflammed tissues [24].

The membrane ion channel activated by capsaicin is unique and is insensitive to conventional calcium and sodium ion-channel blockers such as the dihydropyridines, $\omega$-conotoxin and tetrodotoxin, respectively [9]. In keeping with this, capsaicin-induced activation of peripheral nociceptors was unaffected by calcium channel blocking agents [10]. The capsaicin-activated ion channel may be further distinguished by the polyvalent cationic dye ruthenium red. Thus, the capsaicin-induced accumulation of calcium by sensory neurons is prevented by ruthenium red [9], probably resulting from a block of the capsaicin-activated ion channel [25]. Ruthenium red also appears to be highly selective since it attenuates the activation of nociceptors and the release of sensory neuropeptide by capsaicin but not by other stimulants [25–27]. Capsaicin also produces an activation of a number of biochemical systems. It increases cellular cGMP, diacylglycerol, and inositol trisphosphate turnover, and stimulates arachidonic acid release [9, 28]. However, these events are secondary to calcium entry and do not play a role in the initial activation of sensory neurons by capsaicin.

The excitability of sensory neurons and their sensitivity to capsaicin are increased by nerve growth factor(s) [29]. The physiological relationship of NGF and sensory neurons is not well understood though the production of NGF is increased in inflamed tissues [30] and NGF pretreatment induces hyperalgesia [31] as well as long-term changes in phenotypic expression in sensory neurons. The latter results in the increased synthesis of a number of sensory neuropeptides [29, 32] including substance P and CGRP. In turn, the production of NGF from fibroblasts and Schwann cells [33] is stimulated by substance P-induced release of cytokines such as interleukin-1 [33, 34].

Another functionally important aspect of capsaicin-induced activation of sensory neurons is the release of neurochemicals from peripheral or central nerve terminals [2, 3]. Under physiological conditions the release mechanisms are coupled to voltage-activated calcium channels. However, capsaicin-evoked release is due almost entirely to calcium entry via capsaicin-activated cation channels [2, 3, 35]. It is significant, therefore, that the entry of calcium via these channels subsequently inhibits the voltage-dependent calcium currents [12] with the resultant attenuation of depolarization-induced (via nerve stimulation) neurotransmitter release. The inhibition of release of neuropeptides or other neurotransmitters from central and peripheral terminals is a mechanistic explanation for the analgesic and anti-inflammatory effect of capcaicin (see later). This effect of capsaicin is unlikely to be due to a rapidly reversible process such as calcium-dependent inactivation of membrane calcium permeability. Rather, the longer lasting effect may be due to another calcium-dependent process involving proteolytic inactivation of calcium channel protein. A similar mechanism may contribute to capsaicin-induced desensitization [12, 35] (see later).

*Capsaicin-induced "desensitization"*

Several processes are involved in capsaicin-induced desensitization which is seen as a loss of effectiveness following repeated exposure of tissues to capsaicin. In sensory neurons at least two mechanisms, operating with different time courses and at different membrane potentials, have been identified recently [36]. One process depends on the influx of calcium ions, while another, slower mechanism, appears to be independent of calcium. Nociceptors also show several types of desensitization to capsaicin. Low concentrations of capsaicin induce a loss of sensitivity to capsaicin without impairing responses to other noxious stimuli [10]. Moreover, selective desensitization to capsaicin occurs in the absence of extracellular calcium or even overt nociceptor activation in the absence of sodium ions.

It is possible that this form of desensitization may involve affinity changes in the capsaicin receptor or an uncoupling of the receptor–ion channel complex. This selective desensitization to capsaicin is unlikely to account for the acute antinociceptive effects of capsaicin.

Capsaicin also produces a prolonged block of conduction in some C-fibres [5, 10, 11, 37] and a loss of chemical sensitivity due to an impairment of signal transduction at the afferent nerve terminal [10]. The extent of this depends on the exact concentration and contact time with capsaicin. This would account for the non-specific desensitization in which sensitivity to capsaicin is lost and that to other chemical and physical noxious stimuli is attenuated. The exact mechanisms are unclear by there may be a combination of calcium-independent [37] as well as calcium-coupled inactivation processes. Osmotic changes, due to the accumulation of intracellular ions [9, 11], may also contribute. Such mechanisms may also account for the ultrastructural changes and loss of function in peptide containing afferent nerve endings. This has been suggested as an explanation for one form of desensitization, especially when peptide release was used as a measure of capsaicin-induced nerve activation [38]. It is possible that this type of "desensitization" of peripheral nociceptors may be involved in the reversible reduction of neurogenic inflammation produced by repeated topical administration of capsaicin to the skin [39].

Finally, a selective sensory neurotoxicity [1, 9] may be brought about by exposure to high concentrations of capsaicin. As before several mechanisms have been implicated. Osmotic changes [11, 19], accompanied by inhibition of axoplasmic transport [40], lead to impaired functioning of intracellular organelles. Cell degeneration and lysis may be brought about by an accumulation of sodium chloride while enzyme-related cellular damage may be triggered by the rise in intracellular calcium [11, 19]. However, neurotoxic actions are unlikely to underlie either the acute antinociceptive or anti-inflammatory actions of capsaicin. Both of these effects last a few hours, are completely reversible, and show the characteristic functional changes without evidence of neurodegeneration.

*Capsaicin-induced antinociception*

Systemic capsaicin produces an acute anti-nociceptive effect in a number of conventional tests [15, 41, 42]. The mechanism of antinociception is still unclear, but the phenomenon is reversible, it does not involve a neurotoxic effect, it is clearly unrelated to depletion of neuropeptides from afferent nerves [43], and it does not appear to involve a peripheral mechanism of action. Thus, studies using *in vitro* models have suggested that relatively high concentrations of capsaicin are required to inactive peripheral nociceptors [10]. Such concentrations are not likely to be achieved in peripheral tissue following an acute antinociceptive dose of capsaicin [44]. Indeed, antinociception appears to be due to an effect on capsaicin receptors localized on the central terminals of C-neurons in the spinal cord [22, 45, 46].

In keeping with this, small systemic doses of capsaicin, previously found to be effective in behavioral studies, reversibly depressed C-fibre evoked firing of doral horn neurons [44, 45]. In addition, C-fibre evoked firing was depressed by spinal intrathecal administrations of capsaicin in amounts found to be present in the spinal cord following systemic administration. Furthermore, systemic administration of the antagonist capsazepine reduced the antinociceptive effect of systemic capsaicin. But most significantly, intrathecally administered capsazepine attenuated the anti-nociceptive effect of systemic capsaicin [22]. This would strongly indicate penetration of capsaicin into the spinal cord and an interaction with specific receptors on primary afferent nerve terminals. As indicated earlier, antinociception may result from capsaicin-induced activation of nerve terminals followed by the inactivation of voltage gated calcium channels. The operation of these channels is necessary for continued transmitter release in the spinal cord following depolarizing stimuli to peripheral nociceptors. This hypothesis is further supported by the findings that spinal administration of capsaicin inhibits neuropeptide release from sensory nerve terminals in the spinal cord [45]. Interestingly, acute systemic or local administration of the antagonist capsazepine does not alter the activity of nociceptors or their responses to noxious stimuli [22]. This would suggest that a capsaicin-like molecule is not involved in conditions of acute pain.

Though capsaicin produces analgesia and anti-inflammatory activity following systemic administration, these effects have only been demonstrated in laboratory animals. However, capsaicin has been used by local administration to treat a number of painful clinical conditions [6] including cluster headache, post-mastectomy pain, reflex sympathetic dystrophy pain, the pain of post-herpetic neuralgia, diabetic neuropathy and rheumatoid arthritis [47]. A major drawback to the therapeutic usage of capsaicin has been the initial pain and discomfort on first administration. This can be made more tolerable with local anaesthesia. However, analogues of capsaicin have now been developed in which this algogenic property has been minimized. For example, in laboratory tests, olvanil (Fig. 1) has *in vivo* analgesic potency similar to that of capsaicin [41, 45] but lacks the stimulatory effects of capsaicin both *in vitro* and *in vivo* [45]. Mechanistic studies suggest that like capsaicin the antinociception produced by systemic olvanil may be due to blockade of spinal nociceptive neurotransmission following the inhibition of sensory neuropeptide release from primary afferent nerve terminals [45]. A similar mechanism of nerve terminal inactivation can be postulated for olvanil as that suggested for capsaicin. Thus, even though olvanil may produce a slow depolarization, this is insufficient to initiate a high degree of nociceptor activation. But nonetheless, an intracellular accumulation of calcium results in the inactivation of voltage gated calcium channels. The separation between analgesic efficacy and the algogenic action of capsaicin-like compounds is regarded favourably for the development of a clinically useful analgesic with a novel mechanism of action.

*Summary*

Capsaicin activates poorly myelinated primary afferent neurons, many of which are polymodal nociceptors. Activation is accompanied by membrane depolarization and the opening of a unique, cation-selective, ion channel which can be blocked by the polyvalent dye ruthenium red. The capsaicin-induced activation is mimicked by resiniferatoxin, a potent analogue, and by low pH. Activation is mediated by a specific membrane receptor which can be selectively and competitively antagonized by capsazepine. Repetitive administration of capsaicin produces a desensitization and an inactivation of sensory neurons. Several mechanisms are involved including receptor inactivation, block of voltage activated calcium channels, intracellular accumulation of ions leading to osmotic changes, and activation of proteolytic enzyme processes. Systemic and topical capsaicin produces a reversible antinociceptive and anti-inflammatory action after an initial undesirable algesic effect. Capsaicin analogues, such as olvanil, have similar properties with minimal initial algesic activity. Antinociception produced by capsaicin does not involve neurotoxicity, sensory neuropeptide depletion or activity at peripheral receptors; rather, systemic capsaicin produces antinociception by activating capsaicin receptors on afferent nerve terminals in the spinal cord. Spinal neurotransmission is blocked by a prolonged inactivation of sensory neurotransmitter release. However, local or topical applications of capsaicin block C-fibre conduction and inactive neuropeptide release from peripheral nerve endings. These mechanisms account for localized antinociception and the reduction of neurogenic inflammation, respectively.

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