Capsaicin and pain mechanisms

J. Winter, S. Bevan and E. A. Campbell

Selective actions of capsaicin

Capsaicin, the active ingredient in hot chilli peppers, has selective actions on unmyelinated C-fibres and thinly myelinated A primary sensory neurones [37, 100] (Table 1). Most capsaicin-sensitive fibres are polymodal nociceptors which respond to a range of sensory stimuli including noxious pressure, heat and chemical irritants [51, 100], and are the most abundant class of nociceptive fibre. Nociceptive neurones are likely to release glutamate as a rapid central neurotransmitter, and also express neuropeptides such as calcitonin gene-related peptide (CGRP), substance P, neurokinin A and somatostatin which can be released into the spinal cord during intense stimulation [103]. The tachykinins (e.g. substance P and neurokinin A) and excitatory amino acids (EAAs) (e.g. glutamate) cooperate and are thought to increase synaptic activation of dorsal horn neurones via EAA receptors [103]. Noxious stimulation in the peripheral nervous system results in long-term increases in spinal excitability which may contribute to central mechanisms of allodynia and hyperalgesia [103]. Much of the neuropeptide synthesized in the dorsal root ganglion (DRG) cell body is actually exported peripherally rather than centrally. In peripheral nerve peptide release can contribute to neurogenic inflammation.

Although initial local application of capsaicin in humans is algesic, repeated application leads to desensitization, and high concentrations can block C-fibre conduction and result in long-lasting sensory deficits. These properties of capsaicin may explain its efficacy in treating some painful conditions in humans, for example cluster headache, reflex sympathetic dystrophy, post-mastectomy pain, post-herpetic neuralgia and diabetic neuropathy.

The capsaicin receptor/channel

Most mechanistic studies of capsaicin-induced activation of nociceptive neurones have been made using cultured sensory neurones and isolated nerves in vivo. 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, 31, 115]. The capsaicin-induced accumulation of calcium ions or the flux of radiolabelled ions such as rubidium (in place of potassium) and guanidinium (in place of sodium) has been exploited to quantify the effects of capsaicin-like molecules [115]. Cultured DRG from avian species do not respond to capsaicin with such ion fluxes, and birds are insensitive to capsaicin and will eat chillies [115].

The membrane ion channel activated by capsaicin is unique and is insensitive to conventional calcium and sodium ion-channel blockers such as the dihydropyridines, -conotoxin and tetrodotoxin respectively [5, 115]. It is blocked, however, by ruthenium red [5, 115]. Ruthenium red appears to be relatively selective in its actions at low concentrations since it attenuates the effects (activation of nociceptors and release of sensory neuropeptide) induced by capsaicin but not other sensory nerve stimulants such as bradykinin [2, 34, 69]. Capsaicin activates a number of biochemical systems and increases the concentration of cellular cGMP, diacylglycerol [33, 36, 115] and nitric oxide [4], and stimulates inositol tris-phosphate turnover, and arachidonic acid release [114]. However all these biochemical events are secondary to calcium entry and do not play a role in the initial activation of sensory neurones by capsaicin.

CAPSAICIN ANALOGUES

The biological effects of capsaicin are dose dependent. This fact, together with structure activity data from a range of capsaicin analogues, points to a specific membrane receptor for capsaicin. The best evidence for the existence of a receptor comes from capsazepine (fig. 1), a highly selective competitive capsaicin antagonist which inhibits [6] the excitatory effects of capsaicin in both in vivo and in vitro experiments. Capsazepine itself does not appear to be analgesic [82] which argues against the existence of an endogenous activator of the capsaicin channel that binds at the same site as capsaicin. In fact it seems that capsaicin analogues must have some agonistic activity to show efficacy as analgesics. Two examples are olvanil (NE19550) and nuvanil.
Table 1. Subsets of cutaneous afferent units excited by capsaicin. Modified from Szolcsányi [100]. Data from rabbit, rat, cat or human studies. Application of capsaicin is either by close arterial injection, intradermal or topical.

<table>
<thead>
<tr>
<th>C-afferents</th>
<th>Excitation by capsaicin</th>
<th>A-afferents</th>
<th>Excitation by capsaicin</th>
<th>A-afferents</th>
<th>Excitation by capsaicin</th>
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<tr>
<td>Mechanoheat</td>
<td>Mechanoheat</td>
<td>G-hair</td>
<td>Field</td>
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<tr>
<td>High threshold mechanoreceptor</td>
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<tr>
<td>Low threshold mechanoreceptor</td>
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<tr>
<td>Mechanosensitive (chemonociceptor)</td>
<td>Cold</td>
<td>SA 11</td>
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**Figure 1** Structures of capsaicin and analogues.

PROTONS

Low extracellular pH can stimulate some sensory neurones by opening ion channels [5]. Recent evidence suggests that one type of response to low pH (elevation of the concentration of protons) is via activation of the capsaicin channel itself, suggesting that protons may be the endogenous activators of these channels [7]. The pH of ischaemic or inflamed tissue can fall into the range that directly activates capsaicin-operated channels, and contribute to the pain which can accompany these pathological conditions [5]. Both capsaizpine and ruthenium red block some proton and capsaicin-evoked responses, for example, smooth muscle contraction [66], CGRP release from smooth and skeletal muscles (see e.g. Santicioli and colleagues [88]) and nasal irritation, consistent with the hypothesis that capsaicin and protons operate via the same mechanism [5]. In cultured DRG neurones, however, capsaizpine blocks capsaicin-induced but not proton-induced ion fluxes [5]. It remains to be determined whether the protons open capsaicin-operated channels directly or act indirectly via the release of another mediator.

REGULATION OF CHANNEL DENSITY

Capsaicin sensitivity itself is dependent on the continued presence of nerve growth factor (NGF) in adult DRG cultures [112]. As expected, the sustained proton evoked current and RTX binding are also NGF regulated in culture [7, 112]. In vivo, sciatic nerve section or systemic treatment of animals with capsaicin, which results in a chemical axotomy are both treatments which are likely to deprive DRG neurones of their normal supply of retrogradely transported NGF from peripheral targets. In both cases capsaicin sensitivity decreases. This phenomenon is probably not due to death of NGF-deprived DRG neurones [111, 113 and Woolf, Hu-Tsai and Winter, unpublished observations]. During development, the majority of DRG sensory neurones require NGF for survival, whereas in the adult animal NGF has a more modulatory role and is not needed for survival [58]. Recent studies have shown a key role for NGF in inflammatory hyperalgesia [56, 116]. Concentrations of NGF increase in inflamed tissue.
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[56]. Antibodies that neutralize NGF completely inhibit development or reverse the established hyperalgesia (both mechanical and thermal) that follow an injection of complete Freund's adjuvant (CFA) into the rat paw [116]. In vivo and in vitro studies have shown that NGF regulates several characteristics of nociceptive neurones, including the content of the neuropeptides substance P and CGRP [57, 113] as well as capsaicin sensitivity. The contribution of NGF-dependent upregulation of capsaicin/proton sensitivity to inflammatory hyper-sensitivity is presently unknown.

DESENSITIZATION

The ability of capsaicin to desensitize nociceptive neurones has been well documented [45]. However, two distinct phenomena have been reported under the general heading of desensitization. The first phenomenon is a classic pharmacological desensitization where prolonged or repeated applications of capsaicin lead to a progressive decline in the size of subsequent responses to capsaicin. We propose that the term desensitization be reserved for this specific effect. The second phenomenon is "functional-desensitization", where a challenge with capsaicin leads to a reduction or loss of responsiveness of the neurone to other stimuli. The two phenomena occur often occur together but can be separated when low concentrations of capsaicin are employed. Under these conditions, the responsiveness to capsaicin is reduced or lost selectively and responses to other types of noxious or innocuous stimuli are unchanged [33]. The functional desensitization seen with higher concentrations of capsaicin is believed to be the basis for the analgesic and anti-inflammatory effects of capsaicin.

The process of desensitization appears to be calcium-dependent and little or no desensitization is seen when calcium is removed from the extracellular medium [21, 120]. It seems likely that the increase in intracellular Ca2+ concentration evoked by capsaicin promotes desensitization by stimulating a calcium- and calmodulin-dependent cytosolic enzyme, protein phosphatase 2B (calcineurin). Calcineurin is inhibited by a complex of cyclosporin A and its cytoplasmic binding protein cyclophilin [59] and capsaicin desensitization is almost abolished when the cyclosporin-cyclophilin complex is introduced into the cytoplasm of rat sensory neurones [119]. Conversely, treatments that raised the intracellular concentrations of cyclic AMP increased capsaicin responses in sensory neurones [85]. These findings suggest that sensitivity to capsaicin is regulated by phosphorylation of a key intracellular protein which could be the receptor/ion channel itself or an associated protein. Activation of calcineurin may also be responsible for functional desensitization, which could involve calcium-dependent dephosphorylation of other intracellular proteins such as ion channels or enzymes. This hypothesis is consistent with the observations that capsaicin-induced functional desensitization requires the presence of extracellular calcium [89] and is blocked by the capsaicin antagonist, ruthenium red [2, 67].

Capsaicin stimulates the release of glutamate and neuropeptides (GCRP, neurokinin A and substance P) from the peripheral and central terminals of sensory neurones [29, 39, 53, 60, 61, 62, 68]. This release is a direct consequence of the agonist action of capsaicin and occurs by two distinct mechanisms. The influx of calcium through capsaicin-activated ion channels triggers release independent of action potential generation and propagation. The depolarization evoked by capsaicin also generates action potentials that propagate and activate distant regions of the nerve to release glutamate and neuropeptides. Although capsaicin initially stimulates neuropeptide release, it has a longer-term, inhibitory effect which is one likely mechanism for its analgesic and anti-inflammatory actions [14].

After capsaicin treatment, noxious stimuli no longer release glutamate and neuropeptides despite the presence of near normal levels of neuropeptides in the nerves [3, 8, 76, 101]. This inhibitory effect of capsaicin has been attributed to inhibition of the voltage-gated calcium channels [9, 31, 83, 87], which are responsible for the normal, nerve-evoked release of transmitters from the central and peripheral terminals. A block of transmitter release would inhibit the transmission of noxious signals between nociceptive sensory neurones and spinal cord neurones and reduce or eliminate neurogenic inflammation evoked by neuropeptide release from the peripheral nerve terminals.

There have been several reports that capsaicin inhibits voltage-activated calcium currents. Capsaicin inhibits these currents in rat DRG neurones by a mechanism that involves a capsaicin-evoked influx of calcium with a resultant increase in intracellular free calcium concentration [9, 31, 87]. The inhibitory mechanism has not been fully elucidated but is likely to involve activation of an, as yet, unidentified calcium-dependent process. Some metabolic modification of a key molecule, perhaps the ion channels themselves, is suggested by the finding that the inhibition outlasts the period of agonism by capsaicin. This mechanism means that the analgesic and anti-inflammatory effects of capsaicin are restricted to capsaicin-sensitive neurones and occur at the low concentrations required for agonism. Other mechanisms of functional nerve block, such as depolarization block of action potentials, may also contribute to the cell- and agonism-specific effects of capsaicin.

DEGENERATION / NEUROTOXICITY

Capsaicin has a spectrum of effects on sensory neurones ranging from excitation to cell death. Many DRG neurones degenerate following neonatal capsaicin treatment. The mechanisms of capsaicin-induced neurotoxicity have been studied in vitro in DRG neurones cultured from neonatal animals [114]. The damage is partially osmotic and partially through calcium entry, causing activation of calcium-sensitive proteases among other mechanisms [114]. In vivo the severity of these effects depends on factors such as the age of animal at the time of treatment, and the route of administration, as well as
the dose of capsaicin used. Systemic injection of neonatal rats kills many DRG neurones [47]. In adult rats, many C-fibre terminals degenerate [22, 23] after large systemic doses of capsaicin, but most cell bodies survive to respond vigorously to this “chemical axotomy” by attempting to regenerate [110, 112]. After perineural application of capsaicin, C-fibres degenerate distally and extensive axonal sprouting can be seen from the proximal nerve [63, 84, 112]. Levels of the growth-associated protein (GAP-43) and its messenger RNA increase, and the ability to form neurites in culture increases dramatically if the cells are taken from capsaicin-pretreated animals [110, 112]. Although the neurones with capsaicin-damaged axons attempt to regenerate, they do not reinnervate their targets in vivo, and the sensory deficit is essentially permanent. Following systemic capsaicin treatments, neurodegeneration can also be seen by a silver staining method in parts of the brain [86]. Capsaicin treatment also causes depletion of the neuropeptides substance P and CGRP, and the enzyme fluoride-resistant acid phosphatase (FRAP) from the DRG neurones, and appearance of vasoactive intestinal peptide (VIP), similar to the effects of surgical axotomy [46, 112].

**Summary of mechanism of action of capsaicin (see fig. 2)**

Desensitization is a capsaicin-induced loss of responsiveness to further capsaicin treatment. It is reversible. Desensitization is calcium dependent and probably involves activation of a phosphatase which inactivates the capsaicin channel.

Functional desensitization is a loss of sensitivity to a range of noxious stimuli and underlies the analgesic effects of capsaicin. Functional desensitization is reversible and may also depend on calcium-dependent dephosphorylation of other intracellular proteins such as enzymes or ion channels.

Neurotoxicity is induced by high doses of capsaicin. Neuronal damage such as axon and terminal degeneration and impaired nociception tends to be irreversible, as regeneration does not take place even if the cell bodies of capsaicin-sensitive neurones survive. Both osmotic lysis and action of calcium-dependent proteases may play a part.

**In vivo studies—hyperalgesia and analgesia**

**ACUTE PAIN**

**Animal studies—systemic**

As outlined above capsaicin mediates its actions through a specific membrane receptor. This results in an initial excitation of sensory neurones followed by a period of insensitivity to noxious stimuli. The time course of this effect ranges from a few hours to several months in adult rats receiving either small acute doses (1–10 mg kg\(^{-1}\) s.c.) or larger doses which deplete unmyelinated primary afferent neurones [47] (single dose of 50 mg kg\(^{-1}\) up to cumulative doses of 950 mg kg\(^{-1}\) in total). In such high doses capsaicin is neurotoxic when administered to neonatal animals and hence the resultant effects on sensitivity to noxious stimuli can be lifelong though the results from analgesia tests are conflicting.

In adult rats that have been treated neonatally with capsaicin, analgesia to noxious mechanical, chemical stimuli, or both has been noted by several groups [38, 42, 80]. In contrast, the responses to a thermal challenge are not so consistent, with some groups reporting an increase in thermal nociceptive thresholds [40, 80] while others saw no change [19, 42]. In mice similar results were noted, with significant analgesia to chemical [42] but not to thermal stimuli [40, 42]. Nagy and van der Kooy [80] have suggested that the variability in results may reflect either the different dosing regimens which have been employed (number of applications/concentrations used) or the considerable variability in responsiveness which has been noted after administration of single high doses of capsaicin to neonatal animals.

![Figure 2](image-url) Scheme showing some mechanisms of action for capsaicin. Broken arrows indicate the more speculative pathways.
Similar results are obtained following systemic treatment of adult animals with capsaicin (35–950 mg kg\(^{-1}\) s.c.). Although earlier studies suggested that such doses produce mitochondrial damage [50] and sensory neuropeptide depletion without nerve fibre degeneration [49, 99] more recent studies show C-fibre terminal loss [22, 23]. Animals showed a clear reduction in chemical and mechanical thresholds [44] and an increase [13, 40], no change or a small reduction [44] in thermal thresholds.

When much lower doses are used (1–10 mg kg\(^{-1}\) s.c.) short-lasting (a few hours) analgesic and also anti-inflammatory activity have been observed in a variety of animal models, both acute and chronic [14, 15, 43]. However, the potential therapeutic usefulness in humans of such a treatment is limited by low oral availability and the narrow window between the doses required to show analgesic activity and those which produce side effects such as hyperthermia.

**Animal studies—local**

The limited potential for the use of systemically administered capsaicin has led clinicians to use topical application of capsaicin in their clinical studies. Studies in animals using local or topical application yielded conflicting results. A reduction, an increase or no effect on nociceptive thresholds following topical skin application of capsaicin in animals has been noted [18, 51, 64, 76].

Much of the variability may relate to the number of application and different vehicles used to apply the capsaicin to the skin and hence possible differences in the rate and extent of skin penetration. It is well known from human studies with topical capsaicin that it often requires days to weeks of treatment to see significant analgesic effects [93, 104]. Kenins [51] reported that local application of capsaicin (1 %) to rat skin resulted in an initial excitation followed by a period of desensitization to noxious chemical, mechanical and thermal stimuli, effects which were highly vehicle dependent. Carter and Francis [18] saw no change in thermal threshold following three times daily application of either 1 % or 5 % capsaicin for 4 days. However, at the end of this study an i.c. injection of 0.1 % capsaicin (3.3 mmol litre\(^{-1}\)) produced a marked increase in withdrawal latencies suggesting that the lack of effect of topically administered capsaicin was the result of poor bioavailability. In contrast three topical applications of 1 % capsaicin over a 24-h period were sufficient to cause a marked reduction in the plasma extravasation evoked by either 5 % capsaicin or antidromic nerve stimulation. Lynn and co-workers [64] noted that a single application of 1 % capsaicin to the skin was sufficient to reduce the vasodilatation evoked by nerve stimulation. Surprisingly the skin levels of substance P, a possible mediator of vasodilatation, were still reduced several days later when the vasodilatory response had returned to normal. Similarly, 2 weeks after intradermal injection of capsaicin, a normal vasodilatory response to antidromic nerve stimulation occurred despite depressed levels of substance P [64]. In contrast, after 10 weeks’ application of either 0.075 % (Axsain, Genderm) or 0.75 % capsaicin cream, McMahon and co-workers [76] showed a significant reduction in the extravasation response to mustard oil with no change in the accumulation of either substance P or CGRP in the ligated sural nerve. These observations suggest that the reduction in vasodilatation response cannot be correlated directly with changes in skin peptide levels.

After topical application of capsaicin to the skin and recording C-fibre activity directly in the saphenous nerve Lynn and co-workers [64] noted a loss of sensitivity to pressure while the sensitivity to heat was lost or enhanced dependent on the vehicle used. McMahon and co-workers [76] were unable to see any thermal analgesia in rat paws even after 10 weeks’ application; in fact the 0.75 % capsaicin cream produced hyperalgesia for the first few weeks of treatment.

The available data suggest a separation between the effects of topical capsaicin on the afferent and efferent function of primary afferent neurones. From the animal studies it seems that the efferent function is more readily inhibited, which implies either a possible involvement of different subpopulations of fibres or suggests that the mechanisms involved in local peptide release are more sensitive to capsaicin than those involved in sensory signal transduction.

**Human volunteer studies**

Topical application or local injection of capsaicin in normal human skin resulted in a concentration-dependent burning sensation and a flare response [17, 48, 94]. Within the area of flare, mechanical and thermal hyperalgesia were apparent (primary hyperalgesia) [17, 94]. Extending beyond the area of flare there was an area of secondary (mechanical) hyperalgesia [36, 54, 94]. Both the acute effects and the hyperalgesia diminished with repeated capsaicin administration.

Repeated application of a 1 % solution of capsaicin over several days to the forearm resulted in a reduction or complete abolition of the flare response evoked by either noxious heat [17] or the chemical irritant, mustard oil [48]. Pain thresholds to both these noxious stimuli were increased in these same subjects. The flare responses to injections of histamine and vasoactive agents such as substance P, VIP and somatostatin were also reduced in capsaicin-pretreated skin [3, 8, 101]. Simone and Ochoa [93] investigated the effect of 8 weeks’ topical treatment with Axsain (0.075 %, Genderm) in normal subjects. Heat-induced pain thresholds, which were initially decreased after 1 day of capsaicin treatment, became elevated by 3.5 C after 6 weeks. There was no change in the thresholds for touch, cold, low temperature or mechanical stimulation. The flare response to histamine was, however, reduced.

Therefore, there is some evidence to support the therapeutic use of topically applied capsaicin. There also appears to be good potential for development of compounds with an improved therapeutic profile compared with capsaicin.
**Arthritis**

**Animal studies**

There is a wealth of information implicating capsaicin-sensitive primary afferent neurones in the inflammation (neurogenic) and hyperalgesia associated with animal models of peripheral inflammation. From these animal studies it is well established that the synovium in joints is richly innervated by peptidergic (substance P)-containing nerve fibres and following induction of arthritis in rats there is an increase in the levels of substance P in the joint [70]. Conversely, neonatal capsaicin treatment or treatment of adult rats with a dose of capsaicin which is known to deplete substance P will reduce the inflammation and joint injury [24, 55]. Injection of substance P or capsaicin into non-inflamed joints will induce a mechanical hyperalgesia which persists for several hours [25, 26] and which can be inhibited by a substance P antagonist while substance P injection into inflamed joints is known to enhance the inflammation [55].

After inflammation it has also been shown that substance P levels are increased in the DRG and this seems to be accompanied by increased axonal transport [32, 116]. The elegant studies of Schaible and co-workers [90] demonstrated that following inflammation the high threshold sensory fibres become sensitized to movement in the normal range and initially insensitive sensory fibres become mechanosensitive and may show spontaneous activity. Thus, these sensory fibres will contribute to the ongoing pain associated with the arthritis and peripherally they will enhance inflammation by release of neuropeptides. As discussed above when capsaicin is used systemically in low doses short-lasting analgesia is observed in acute tests. Perkins and Campbell [82] demonstrated that this was also the case in models of monoarticular arthritis in rats induced by uric acid or Freund’s adjuvant injection into the knee where capsaicin (6 mg kg\(^{-1}\)) reversed the mechanical hyperalgesia for several hours, therefore this analgesic effect is not the result of neurotoxicity.

**Human studies**

**Rheumatoid arthritis.** The normal human synovium receives innervation from substance P-immunoreactive fibres which are associated with blood vessels or as free fibres which extend into the intimal layer of the synovial membrane. However, in chronic rheumatoid arthritis the number of free fibres is decreased and there is a reduction in the staining for substance P-containing fibres in the intimal layer [71, 81]. This reduced staining may to some extent reflect increased release as synovial fluid levels of substance P exceed plasma levels in most types of arthritis suggesting direct release into the synovium and synovial fluid [72].

To date the clinical studies using topically applied capsaicin report conflicting results. Deal and co-workers [28] reported significant reduction in pain intensity and joint tenderness after 4 weeks of treatment (Zostrix, 0.025 %) in 31 patients with rheumatoid arthritis of the knee. In contrast, McCarthy and McCarty [73] using 0.075 % capsaicin cream saw no significant improvement in seven patients with rheumatoid arthritis of the hands. In support of the findings of the former study Weisman and co-workers [109] have recently reported that application of topical capsaicin (0.075 %) for 6 weeks produced a reduction in inflammatory mediators, including substance P, in the synovial fluid of patients with rheumatoid arthritis.

**Osteoarthritis.** As in the case of rheumatoid arthritis substance P has also been implicated in the pathophysiology of osteoarthritis. Substance P concentrations are increased in the plasma and synovial tissue of patients with osteoarthritis [72, 78], Substance P has also been suggested to enhance cartilage destruction [1].

Two earlier double-blind studies demonstrated a significant improvement in pain relief following treatment with capsaicin cream in patients with osteoarthritis of the knee (0.025 % for weeks, 70 patients) [28] and hand (0.075 %, 14 patients) [73]. A more recent multicentre double-blind trial involved 113 patients with osteoarthritis of the knee, ankle, elbow, wrist or shoulder [1]. In patients given 0.025 % capsaicin cream four times daily for 12 weeks 81 % using capsaicin improved compared with 54 % receiving vehicle based on the physician’s evaluation with similar results obtained when comparing the data from the patients’ evaluation (visual analogue scale).

**Neuropathic pain**

**Animal studies**

The majority of clinical trials using capsaicin have investigated its analgesic efficacy after topical application in conditions of neuropathic pain. There is little experimental evidence, however, on its effects in animal models of neuropathic pain. Adult rats which had been neonatally treated with capsaicin (50 mg kg\(^{-1}\) s.c.), did not develop the thermal hyperalgesia which normally arises after either chronic constriction injury or partial ligation of the sciatic nerve [77, 91]. In contrast, in the same animals which had received a partial ligation, mechanical hyperaesthesia and allodynia developed as normal [91]. Yamamoto and Yaksh [117] administered capsaicin intrathecally (15 μg/15 μL) 2 days after constriction injury and determined thermal paw withdrawal thresholds to a thermal stimulus 5 days later. Although the results were confusing it was clear that the capsaicin-pretreated animals showed no significant hyperalgesia on the ligated paw compared with vehicle-treated animals. Kim and co-workers [52] applied capsaicin (0.05–2.0 %) directly around the nerve 1 week after ligation, and studied thermal withdrawal latencies for up to 8 weeks. Animals treated with doses of 0.1 % or higher showed a significant, dose-dependent increase in withdrawal latencies on the ligated paw compared with the contralateral paw.
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These studies, therefore, implicate a role for capsaicin-sensitive nerves in the thermal hyperalgesia which develops in these animals. However, the doses used are considerably higher than the 0.025–0.075 % topical capsaicin cream which is used clinically.

**Human studies**

Despite the limited experimental evidence from animal studies, the possible therapeutic usefulness of topically applied capsaicin has been the subject of many clinical trials in the area of neuropathic pain (see table 2). In general, conditions involving neuronal damage and subsequent development of neuropathic pain respond poorly to conventional analgesics. For this reason the possibility of a novel approach to the treatment of such patients has received considerable attention in the past few years. Clinical trials (see table 2) demonstrating significant improvement with topical capsaicin have been carried out in patients with post-mastectomy pain, stump pain, reflex sympathetic dystrophy, oral neuropathic pain and trigeminal neuralgia. However, the greatest numbers of patients studied have been in the fields of diabetic neuropathy and post-herpetic neuralgia where the efficacy reported in the early trials has led to subsequent large multicentre studies.

In small numbers of patients the early reports demonstrated a significant improvement in pain scores after treatment with capsaicin. In general the effects of capsaicin took several weeks to develop and in most studies there was a significant number of patients who dropped out in the early weeks owing to the irritant properties of capsaicin which produced a burning pain following application. Therefore, although some of the trials claim to be double blind this effect of capsaicin will clearly distinguish it from placebo. With repeated application, however, this unwanted side effect diminished.

The Capsaicin Study Group [16] studied a total of 277 patients (138 capsaicin 0.075 %, 139 placebo) with diabetic neuropathy and reported significant improvement in all measures (pain, walking, working, sleeping) after administration of capsaicin four times daily for up to 8 weeks. Most studies have been of a similar duration although Watson and co-workers [108] followed 83 patients with post-herpetic neuralgia for up to 2 years and found that in 86 % of the subjects the improvement in pain scores was either maintained or further enhanced with no serious adverse effects.

**Table 2**

Clinical trials with topical or locally administered capsaicin where significant improvement in pain scores was demonstrated compared with vehicle. The concentration of the capsaicin cream used is given together with the duration of treatment in brackets (d, days; wk, weeks; mth, months; yr, years).

<table>
<thead>
<tr>
<th>Condition</th>
<th>Dose of capsaicin</th>
<th>Reference</th>
</tr>
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<tbody>
<tr>
<td>Post-herpetic neuralgia</td>
<td>0.075 % (6 wk)</td>
<td>Bernstein and colleagues [4a]</td>
</tr>
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<td></td>
<td>0.025 % (4 wk)</td>
<td>Watson and colleagues [107a]</td>
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<td></td>
<td>0.1 mg/ml (5 wk)</td>
<td>Bjerring and colleagues [8a]</td>
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<td></td>
<td>0.025 % (8 wk)</td>
<td>Peikert and colleagues [90a]</td>
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<tr>
<td></td>
<td>0.025 % (4 wk)</td>
<td>Srebnik and Brenner [94a]</td>
</tr>
<tr>
<td></td>
<td>0.075 % (6 wk)</td>
<td>Watson and colleagues [108]</td>
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<td></td>
<td>0.075 % (2 yr)</td>
<td>Watson and colleagues [108]</td>
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<td>Diabetic neuropathy</td>
<td>0.075 % (8 wk)</td>
<td>Scheffler and colleagues [90a]</td>
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<td>0.075 % (8 wk)</td>
<td>Capsaicin Study Group [16]</td>
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<td></td>
<td>0.075 % (6 wk)</td>
<td>Watson and Evans [107a]</td>
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<td></td>
<td>0.075 % (10–24 wk)</td>
<td>Sinoff and Hant [94a]</td>
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<td></td>
<td>0.025 % (1 wk)</td>
<td>Rayner and colleagues [85a]</td>
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<td>0.025 % (3 wk)</td>
<td>Cheshire and Snyder [20a]</td>
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<td></td>
<td>0.025 % (10–24 wk)</td>
<td>Sinoff and Hart [94a]</td>
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<td>Stump pain</td>
<td>0.05 % (15–20 d)</td>
<td>Fusco and colleagues [38a]</td>
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<td>0.025 % (5 mth)</td>
<td>Epstein and Marcove [37b]</td>
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<td>Reflex sympathetic dystrophy</td>
<td>0.025 % (3 wk)</td>
<td>Deal and colleagues [38]</td>
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<td>0.025 % (12 wk)</td>
<td>McCarthy and McCarthy [73]</td>
</tr>
<tr>
<td></td>
<td>0.025 % (4 wk)</td>
<td>Altman and colleagues [1]</td>
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<td>Trigeminal neuralgia</td>
<td>0.075 % (10–24 wk)</td>
<td>Sinoff and Hart [94a]</td>
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<tr>
<td>Oral neuropathic pain</td>
<td>0.025 % (10–24 wk)</td>
<td>Sinoff and Hart [94a]</td>
</tr>
<tr>
<td>Osteoarthritis</td>
<td>0.025 % (4 wk)</td>
<td>Deal and colleagues [38]</td>
</tr>
<tr>
<td></td>
<td>0.075 % (4 wk)</td>
<td>McCarthy and McCarthy [73]</td>
</tr>
<tr>
<td></td>
<td>0.025 % (12 wk)</td>
<td>Altman and colleagues [1]</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>0.025 % (4 wk)</td>
<td>Deal and colleagues [38]</td>
</tr>
<tr>
<td>Cluster headache</td>
<td>100 µl of 10 mmol litre$^{-1}$ (5 d)</td>
<td>Sicuteri and colleagues [91a]</td>
</tr>
<tr>
<td></td>
<td>100 µl of 10 mmol litre$^{-1}$ (7 d)</td>
<td>Fusco and colleagues [38a]</td>
</tr>
<tr>
<td></td>
<td>0.025 % (7 d)</td>
<td>Marks and colleagues [71a]</td>
</tr>
<tr>
<td>Fibromyalgia</td>
<td>0.025 % (4 wk)</td>
<td>McCarty and colleagues [74]</td>
</tr>
</tbody>
</table>

**OTHER CLINICAL INDICATIONS**

There have been several studies reporting the efficacy of nasal application of capsaicin in the treatment of cluster headache (see table 2). Patients applied the capsaicin daily for up to 7 days with a resultant significant improvement compared With placebo and in some cases complete disappearance of symptoms. The mechanism by which capsaicin provides relief in such patients is unknown though substance P containing neurones of the trigeminal nerve have been implicated in the symptomatology of cluster headache.

More recently the efficacy of topical capsaicin has been assessed in the treatment of the pain associated with fibromyalgia (table 2). After 4 weeks’ treatment with 0.025 % capsaicin patients reported significantly less tenderness; however, there was no significant change in the visual analogue scale for
As mentioned above the beneficial effects of capsaicin can take several weeks to develop, therefore in this study perhaps a longer treatment period or the use of 0.075 % capsaicin cream would have shown better efficacy.

One further area which has also received attention is the use of topical capsaicin in the treatment of pruritus. Itch is believed to be mediated by a subset of capsaicin-sensitive nociceptive neurones and blocking C-fibre conduction suppresses itch [65, 75]. In human volunteer studies capsaicin treatment inhibited the itch after histamine and allergen challenge and has subsequently been shown to reduce the itch associated with a variety of clinical conditions (table 3).

The future
Capsaicin analogues
The potential therapeutic usefulness of an analogue of capsaicin which retains its selective action on primary afferent neurones and analgesic activity but is devoid of unwanted side effects has prompted several groups to try to develop novel therapeutic drugs based on capsaicin.

Earlier structure-activity studies suggested that it was not possible to produce an analogue with significant antinociceptive activity but with reduced excitatory effects [41, 98]. The latter group noted that potent analgesic activity could not be separated from a profound hypothemic effect evoked by all of the analogues studied. However, more recent studies have claimed analgesic activity with analogues of capsaicin which lack pungency and have a reduced side-effect profile [11, 12, 20, 92, 118]. Brand and co-workers [11] reported significant thermal and mechanical analgesia and anti-inflammatory activity following administration of NE19550 (olvanil, N-(3-methoxy-4-hydroxy-benzyl) oleamide, fig. 1), an analogue which lacked the acute toxicity of capsaicin. This compound also inhibited both the early and late phases of the formalin response [35] and reduced yeast-induced inflammation in mouse paws [15]. As well as activity in these acute assays this compound also showed dose-dependent analgesic activity in a model of chronic pain, adjuvant-induced monoarthritis [14]. Further modification of this molecule substituting an aminoethoxy group for the hydroxyl group on the aromatic ring (NE21610, nuvanil, fig. 1) was claimed to improve solubility, and make the compound more effective when administered orally while being less irritant to the skin. Results from our own laboratory demonstrated that while NE21610 showed improved oral activity over capsaicin and NE19550, significant analgesia was only seen, at doses which produced profound hypothermia [14].

This compound, NE21610, has also been studied in humans though only with local administration. When given intradermally NE21610 was much less excitatory than capsaicin but was still effective at inhibiting burn-induced hyperalgesia and allodynia [27, 79]. Genderm, the manufacturer that markets the currently available capsaicin creams (Zostrix, Axsain), is also reported to have an analogue in development which is less irritant than capsaicin.

Chen and co-workers [20] described a series of analogues based on substitutions at position 4 on the aromatic ring, a region which Szolcsányi and Jancsó-Gábor [98] highlighted as being essential for pungency. Several of these analogues were non-pungent and showed reduced activation of vagally mediated blood pressure reflexes yet retained marked antinociceptive activity. More recently, Walpole and co-workers [105, 106, 107] reported a series of structure-activity studies based on different parts of the capsaicin molecule and described a rational basis for the design of compounds with increased potency.

### Table 3
Clinical trials with topical administered capsaicin where significant improvement in pruritic symptoms was demonstrated compared with placebo. The concentration of the capsaicin cream used is given together with the duration of treatment in brackets (wk, weeks)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Dose of capsaicin</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psoriasis</td>
<td>0.025% (8 wk)</td>
<td>Kurkcuoglu and Alaybeyi [53a]</td>
</tr>
<tr>
<td></td>
<td>0.025% (6 wk)</td>
<td>Ellis and colleagues [37a]</td>
</tr>
<tr>
<td>Haemodialysis</td>
<td>0.025% (6 wk)</td>
<td>Breneman and colleagues [12a]</td>
</tr>
<tr>
<td>Notalgia paraesthetica</td>
<td>0.025% (6 wk)</td>
<td>Leibsohn [54a]</td>
</tr>
<tr>
<td>Brachioradial pruritus</td>
<td>0.025% / 0.075% (2 wk)</td>
<td>Goodlow and Eaglstein [40a]</td>
</tr>
<tr>
<td></td>
<td>0.025% (3 wk)</td>
<td>Knight and Hayashi [52a]</td>
</tr>
<tr>
<td>Aquagenic pruritus</td>
<td>0.025–1.0 % (4 wk)</td>
<td>Lotti and colleagues [59a]</td>
</tr>
</tbody>
</table>
The data therefore suggest that it may be feasible to develop an analogue with the required profile of antinoceptive activity and minimal unwanted side effects.

Capsaicin antagonist

Recent data with the capsaicin antagonist capsazepine support the hypothesis that some degree of capsaicin-like agonism is essential for a capsaicin analogue to show analgesic activity.

Capsazepine is a novel competitive antagonist of capsaicin which selectively antagonizes capsaicin-induced activation of nociceptors [6, 30, 102]. In animal studies capsazepine showed none of the known side effects of other capsaicin analogues; however, it had no analgesic or anti-inflammatory activity when administered on its own at doses up to 75 mg kg⁻¹, but it was able to inhibit capsaicin-induced, analgesia in both acute and chronic pain models in a dose-dependent manner [82] (fig. 3). This absence of analgesia with capsazepine alone in inflammatory pain models argues against the production of a structurally related capsaicin-like molecule that promotes pain and inflammation by interacting with the capsaicin receptor.

Summary of efficacy of capsaicin and its analogues in vivo

Capsaicin is a cell-specific peripheral analgesic. Agonism, that is ability to open capsaicin-operated channels, is required for efficacy. There is growing evidence for efficacy of capsaicin in a range of pain conditions. A better window between analgesic doses and doses which produce side effects is effective for an orally active therapeutic drug. However, topical applications are effective and without side effects.

References

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45. Dray A, Forbes CA, Burgess GM. Ruthenium red blocks the capsaicin-induced increase in intracellular calcium and activation of membrane currents in sensory neurons, as well as the activation of peripheral nociceptors in vitro. Neuroscience Letters 1990; 110: 52–59.


