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REVIEW ARTICLE

Topical capsaicin for pain management: therapeutic potential and mechanisms of action of the new high-concentration capsaicin 8% patch

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Editor's key points

- Topical capsaicin is used in pain management.
- The mechanism of action (MoA) was thought to be by depletion of substance P.
- A more likely MoA is described as 'defunctionalization', and involves alteration of several mechanisms involved in pain.
- A new higher concentration (8%) patch shows promise in pain management.

Summary. Topical capsaicin formulations are used for pain management. Safety and modest efficacy of low-concentration capsaicin formulations, which require repeated daily self-administration, are supported by meta-analyses of numerous studies. A high-concentration capsaicin 8% patch (Qutenza™) was recently approved in the EU and USA. A single 60-min application in patients with neuropathic pain produced effective pain relief for up to 12 weeks. Advantages of the high-concentration capsaicin patch include longer duration of effect, patient compliance, and low risk for systemic effects or drug–drug interactions. The mechanism of action of topical capsaicin has been ascribed to depletion of substance P. However, experimental and clinical studies show that depletion of substance P from nociceptors is only a correlate of capsaicin treatment and has little, if any, causative role in pain relief. Rather, topical capsaicin acts in the skin to attenuate cutaneous hypersensitivity and reduce pain by a process best described as 'defunctionalization' of nociceptor fibres. Defunctionalization is due to a number of effects that include temporary loss of membrane potential, inability to transport neurotrophic factors leading to altered phenotype, and reversible retraction of epidermal and dermal nerve fibre terminals. Peripheral neuropathic hypersensitivity is mediated by diverse mechanisms, including altered expression of the capsaicin receptor TRPV1 or other key ion channels in affected or intact adjacent peripheral nociceptive nerve fibres, aberrant re-innervation, and collateral sprouting, all of which are defunctionalized by topical capsaicin. Evidence suggests that the utility of topical capsaicin may extend beyond painful peripheral neuropathies.

Keywords: capsaicin; nerve growth factor; neuropathic pain; nociceptor; TRPV1

Topical capsaicin formulations are widely used to manage pain. Low-concentration creams, lotions, and patches intended for daily skin application have been available in most countries since the early 1980s. Prescriptions are usually not needed for these self-administered medicines, which often have not been reviewed formally by drug regulatory authorities. The recent approval in the EU and USA of a prescription-strength high-concentration single-administration capsaicin 8% patch (Qutenza™) with a duration of action over many weeks invites an examination of recent advances in the understanding of capsaicin's mechanism and site of action.

In this review, which does not cover other naturally occurring or synthetic TRPV1 agonists, we discuss the potential utility of topically administered capsaicin for the management of pain in classical peripheral neuropathies and other hypersensitivity disorders, some of which are currently considered as idiopathic. Furthermore, we seek to elucidate the molecular and cellular basis of capsaicin treatment, and clarify misunderstandings, particularly with respect to the involvement of substance P depletion.

Pain management with topical capsaicin

Capsaicin has played an important role in folk medicine, often on the basis of using like to treat like, for example, treating burning pain with a substance which causes burning pain.[1] The first formal report of the pain-reducing properties of topical capsaicin in the West appeared in 1850 as a recommendation to use an alcoholic hot pepper extract on burning or itching extremities.[2] Creams, lotions, and patches containing capsaicin, generally in the range of 0.025–0.1% by weight, are now sold in many countries, often without the requirement

of a prescription, for the management of neuropathic and musculoskeletal pain. Clinical studies of these medications, usually involving three to five topical skin applications per day for periods of 2–6 weeks, have generally suggested modest beneficial effects against various pain syndromes, including post-herpetic neuralgia (PHN), diabetic neuropathy, and chronic musculoskeletal pain.[3 4] Since low-concentration, capsaicin-based products often result in contamination of the patient's environment (clothing, bedding, contact lenses, etc.) and each application may be associated with a burning sensation, poor patient compliance with these products is often cited as a likely contributor to limited efficacy.[5]

In an attempt to evaluate whether pain relief could be achieved by a *single* exposure to a much higher concentration of topical capsaicin, 10 patients with intractable pain syndromes were treated with a compounded high-concentration 5–10% w/w cream.[6] Patients were provided regional anaesthesia for tolerability and airborne contamination of treatment rooms occurred. Based on encouraging results, a high-concentration capsaicin-containing (8%) patch designated NGX-4010 and then given the trade name Qutenza™ was developed and evaluated.[7]

The capsaicin 8% patch is designed to rapidly deliver capsaicin into the skin while minimizing unwanted systemic or environmental exposure of capsaicin to patients and health-care providers. Phase 1 data suggested that a single 60-min patch application was adequate to induce nociceptor defunctionalization, as measured by reversible reduction in intra-epidermal nerve fibres (ENFs), marked by the structural nerve marker protein gene product (PGP) 9.5 immunostaining, and small, reversible alterations in cutaneous nociceptor function.[8 9] Phase 3 studies demonstrated efficacy against PHN[10 11] (Fig. 1) and painful HIV-AN (associated neuropathy).[12] For both neuropathic pain syndromes, efficacy was observed to last for 12 weeks. Blinding was provided by a control patch which contained sufficient capsaicin to induce pain and erythema in a substantial number of subjects.

In 2009, Qutenza™ was approved for the treatment of peripheral neuropathic pain in non-diabetic adults in the EU, and in the USA to manage neuropathic pain associated with PHN.[7] One important aspect of this formulation relative to low-concentration capsaicin formulations is removal of the potential for variability in administration and a lack of patient compliance, as its use occurs under the supervision of a health-care professional, and it requires a single application for 30 or 60 min. Furthermore, the environmental contamination issues associated with home use are avoided.

Capsaicin pharmacology

Capsaicin is a highly selective and potent (low nanomolar affinity) exogenous agonist for the TRPV1 receptor, a transmembrane receptor-ion channel complex which provides integrated responses to temperature, pH, and endogenous lipids.[13] Temperatures of 43°C or higher or acidity of pH of <6.0 can directly activate the channel, but combinations of these two stimuli can activate the channel at substantially lower temperatures or pH values. Numerous putative endogenous agonists for TRPV1 have been identified; these include anandamide, *N*-acyldopamines, other long-chain unsaturated fatty acids, and lipoxygenase compounds such as leukotriene B4 and 12-(*S*) and 15-(*S*)-hydroperoxyeicosatetraenoic acid.[13] Recently, oxidized metabolites of linoleic acid have been added to the list of potential endogenous agonists.[14] Responsiveness of TRPV1 receptors to these activators is also highly regulated by the phosphorylation state of the channel complex, the presence of ancillary proteins, and an ever-growing array of putative allosteric modulators.[15]

When activated by a combination of heat, acidosis, or endogenous/exogenous agonists, TRPV1 may open transiently and initiate depolarization mediated by the influx of sodium and calcium ions. In the nociceptive sensory nerves which selectively express TRPV1 (mostly C- and some Aδ-fibres), depolarization results in action potentials, which propagate into the spinal cord and brain, and may be experienced as warming, burning, stinging, or itching sensations (Fig. 2).

In contrast to transient activation which follows normal environmental stimuli or inflammatory responses to tissue injury, activation of TRPV1-expressing nerve fibres by exposure to a chemically stable exogenous agonist, such as capsaicin, can generate a biochemical signal with a persistent effect. The TRPV1 channel is highly calcium permeable (with a calcium:sodium permeability ratio that starts at about 8:1 and increases to about 25:1 during prolonged capsaicin exposures),[16] which allows significant amounts of

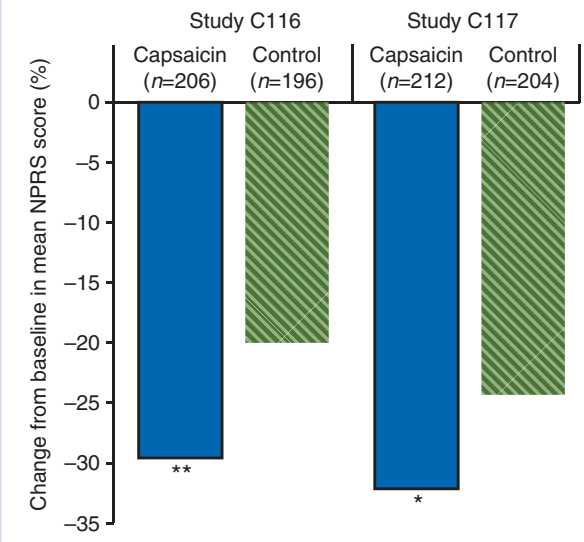

Fig 1 Efficacy of capsaicin 8% patch in post-herpetic neuralgia patients. Per cent change from baseline in mean numeric pain rating scale (NPRS) score during weeks 2–8 (the primary endpoint) in two similarly designed randomized, double-blind, multicentre trials (C116[10] and C117[11]). Capsaicin 8% w/w or control (capsaicin 0.04% w/w) patches were applied once for 60 min to the painful areas and patients were followed for 12 weeks. Mean baseline NPRS scores per group ranged from 5.7 to 6.0. *P=0.011, **P=0.001 *vs* control. Taken from McCormack.[7]