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The Pharmacology and Therapeutic Implications of Capsaicin

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ABSTRACT:

Capsaicin, a naturally occurring chemical found in chilli peppers, is what gives them their characteristically fiery flavour. An odourless fat-soluble chemical, it is quickly absorbed by the skin. Capsaicin's analgesic effects can be attributed to its ability to block the Transient Receptor Potential action channel (subfamily V), type 1 (TRPV1) in small fibre nociceptor neurons. Specifically, it binds to the vanilloid receptor TRPV1, which mediates the combined effects of chemical and mechanical pain inputs at the molecular level.

Using capsaicin topically can help with the discomfort of both diabetic neuropathy and chronic musculoskeletal pain. In patients with bladder hyperactivity, it is used to enlarge the bladder and lessen the frequency of incontinence. When applied to acupuncture points, capsaicin prevents post-operative nausea and vomiting. It has potential as a therapy for pruritis related to renal failure and as a gastric barrier against the side effects of non-steroidal anti-inflammatory drugs. In the future, capsaicin analogues and TRPV1 antagonists may deliver more effective and better tolerated medicinal treatments.

Keywords*:* Pharmacology, Capsaicin

INTRODUCTION:

Natural capsaicin may not be as effective or as well tolerated as synthetic medicines that target the TRPV1 receptor for the treatment of pain and inflammation. Peppers get their spiciness from capsaicin, an alkaloid (capsaicinoid) in the Capsicum family. When it comes into touch with mammalian flesh, it generates a burning sensation. The placental tissues of fruits contain high concentrations of capsaicin, which likely serves as a deterrent to herbivores. Isolated in 1846, its structure was not understood until 1919.[1-4] 1 Capsaicin acts by binding to Transient Receptor Potential receptor Variant 1 (TRPPV1, formerly known as the vanilloid receptor), which is highly expressed in sensory neurons. 2 Heat and extracellular protons are two examples of unpleasant stimuli that activate the TRPV receptor (hydrogen ions). Capsaicin has been shown to release and deplete substance P from afferent nociceptive specific neurons over 20 years ago. 3 Capsaicin stimulates thermoreceptor potential vanilloid (TRPV) receptors in sensory neurons, evoking feelings of heat that can quickly escalate to a burning sensation. Following this, substance P depletion causes tiny

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sensory neurons to become less sensitive, resulting in analgesia.[5-7] Mediators of neurotransmission and inflammation are not released by the sensory nerves, making them less responsive to unpleasant heat and chemical stimuli. New analgesics and anti-inflammatory medications have been created by capitalising on these characteristics. Some forms of chronic pain (including postherpetic neuralgia, musculoskeletal pain, and bladder dysfunction) have benefited from topical administrations of capsaicin and other vanilloids.

Therapeutic compounds with enhanced efficacy and tolerance, including capsaicin analogues and TRPV1 receptor antagonists, are now under investigation.This article's goals are to provide a synopsis of capsaicin's pharmacology, examine the evidence for its present clinical uses, and evaluate potential future therapeutic applications.

Pharmacokinetics

Capsaicin used topically is readily absorbed by the body. When used topically, capsaicin quickly reaches maximum cutaneous concentrations. Preparations made with isopropyl alcohol have higher concentrations than those made with propylene glycol or mineral oil. Capsaicin has a roughly 24-hour half-life.[8] Twelve healthy volunteers were given 3% capsaicin solutions (composed of 55% capsaicin, 35% hydrocapsaicin, and 10% other analogues) in one of three vehicle preparations: 70% isopropyl alcohol, mineral oil, or propylene glycol, which contained 20% alcohol. Once the capsaicinoids were applied, they were identified in the stratum corneum within 1 minute, and the concentrations quickly settled into a steady state. When compared to the mineral oil and propylene glycol preparations, the maximum concentration in the participants who received the 70% isopropyl alcohol preparation was about 3 times higher. This proved that the capsaicinoids were more soluble in the increased amount of alcohol. In all three formulations, the capsaicin half-life was roughly 24 hours. After being injected, capsaicin travels throughout the mouse body, including the central nervous system and the liver. [9]

Vanilloids like capsaicin and thymol bind to the Transient Receptor Potential V1 receptor on neuron membranes (previously known as vanilloid receptor, VR1). Temperature, acidity, pain, and osmolarity are among signals that are received by the TRP receptors.

14 It can be activated directly or indirectly by capsaicin, protons, heat (>43 C), and endogenous lipid molecules known as endovanilloids. 11 TRPV1 is essential for both heat nociception and inflammatory hyperalgesia.[15]

Most small-fibre nociceptive neurons express TRPV1, a ligand-gated, nonselective cation channel. There is a connection between the receptor and a membrane cation channel that is permeable to both calcium and sodium ions. Regular ion channel blockers are ineffective against this channel, but ruthenium red and arginine rich hexapeptides (like dynorphin) are effective. Caterina discovered and cloned the TRPV1 receptor in rats in 1997; this receptor, shared by humans and rodents, comprises of 838 amino acids and has a molecular weight of 95 kDa. 16 Capsaicin's spiciness is communicated to the brain via a heat-sensitive subunit. The deletion of the TRPV1 gene in transgenic animals reduced capsaicin sensitivity and

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thermal hypersensitivity due to inflammation. Vanilloids such as capsaicin bind to the Transient Receptor Potential V1 receptor on the surface of nerve cells (previously known as vanilloid receptor, VR1). TRP receptors are also sensitive to changes in osmolarity, pH, acidosis, and pain.

Direct or indirect activation occurs with the addition of capsaicin, hydrogen ions, temperatures above 43 degrees Celsius, and endogenous lipid molecules known as endovanilloids.[11] Both heat nociception and inflammatory hyperalgesia include TRPV1. [15]

Small fibre nociceptive neurons are particularly rich in TRPV1, a ligand gated nonselective cation channel. There is a connection between the receptor and a membrane cation channel that is permeable to both calcium and sodium ions. Regular ion channel blockers are ineffective against this channel, but ruthenium red and arginine rich hexapeptides (like dynorphin) are effective. Caterina discovered and cloned the TRPV1 receptor in rats in 1997; this receptor, shared by humans and rodents, comprises of 838 amino acids and has a molecular weight of 95 kDa.[16] Capsaicin's spiciness is communicated to the brain via a heat-sensitive subunit. The deletion of the TRPV1 gene in transgenic animals reduced capsaicin sensitivity and thermal hypersensitivity due to inflammation.

Research with a powerful capsaicin counterpart, resiniferatoxin, hints at a different mechanism of analgesia. Resiniferatoxin (RTX) induces a persistent increase in free intracellular calcium levels by activation of TRPV1 receptors, resulting in calcium-induced cytoxicity and selective death of cells expressing TRPV1 receptors. The inflammatory hyperalgesia, neurogenic inflammation, was specifically blocked by deleting TRPV1-bearing nociceptive neurons in single and multiple ganglia, as demonstrated by the work of Karai 19 and colleagues 20.

The preservation of senses of touch, proprioception, high-threshold mechanosensitive nociception, and locomotion points to a selective loss of neurons. In human dorsal root ganglion cells, RTX induced a sustained rise in intracellular calcium in vanilloid-sensitive neurons while having no effect on neighbouring non-TRPV1 carrying neurons. It was proposed by the authors that deleting nociceptive neurons or nerve terminals could be a useful pain control technique.

Capsaicin increases metabolic rate by activating the sympathetic adrenergic nervous system. Capsaicin has been shown to reduce fat mass in the body in a dose-dependent fashion after ingestion. Capsaicin's effects on weight loss have been studied. [21]

Chronic neuropathic pain after herpes zoster is called postherpetic neuralgia (PHN). Patients older than 60 years old have a 1 month incidence of PHN of around 40%. 35 Two randomised, placebo-controlled studies of topical capsaicin for the treatment of pain in PHN36 were recently analysed in a quantitative systematic review. The pooled NNT for topical 0.075% capsaicin was 3.26 (95% CI, 2.26-5.85). The most prevalent side effect was local irritation at the place of application, with a NNH for mild damage of 3.94. (2.5–8.6).

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The NNT for tricyclic antidepressants is 2.64, making them the first choice treatment. Patients with PHN who suffer from neuralgia due to sensitised nociceptors rather than deafferentation of nerves, as described by Hempenstall, may benefit from topical capsaicin as an additional therapy in the early stages of treatment. Patients with deafferentation or sensitization syndromes can be differentiated with the help of a quantitative sensory evaluation, such as the measurement of epidermal neuronal density in a skin biopsy. [16]

There is some evidence that the intercostobrachial nerve injury experienced by 20-40% of patients post-mastectomy or lumpectomy causes the onset of the post-mastectomy pain syndrome. Capsaicin 0.075% applied topically reduced stabbing pain scores by more than 50% in a randomised, parallel-group study of 25 patients, although it had no effect on chronic pain. [23,24] As the relative benefit was only 3.9 (0.5-28), capsaicin did not provide any noticeable benefit.

Alterations in taste perception and searing pain in the tongue or oral mucosa characterise the phenomenon known as "burning mouth," which is often diagnosed on the basis of the patient's description alone, without the benefit of clinical or laboratory testing. There may be a connection to cranial nerve dysfunction. 44 In a clinical research, patients with burning mouth syndrome who took 0.25 percent capsaicin orally for one month fared better than those who took a placebo.

However, one-third of the active group reported experiencing stomach pain, and the severity of these complaints grew as treatment continued. [25]

Gastroprotection

TRPV1-containing nerve fibres are abundant in the digestive tract. There is evidence that TRPV1 receptors have a role in both stomach protection and inflammation. 12 The capsaicin-induced increases in mucosal blood flow and vasodilation are mediated through the secretion of nitric oxide and calcitonin gene-related peptide (CGRP) by cells containing TRPV1. Capsaicin was found to have preventive qualities against gastropathy associated with indomethacin and ethanol in a prospective trial including 84 young, healthy adults. Reduction in baseline stomach acid production was seen at many doses (ED50 for capsaicin of 400 mg). Capsaicin raised the transmucosal potential differential in a dose-dependent manner. In addition, there was a rise in gastric emptying. Capsaicin, given either before or after ethanol, counteracted the effect of the alcohol on the transmucosal potential differential. Microbleeding from indomethacin was decreased by capsaicin. When capsaicin was taken for two weeks before indomethacin, however, there was no difference in bleeding rates. In contrast to capsaicin's desensitising effects, its acute stimulatory actions that cause mucosal hyperaemia have been hypothesised to be responsible for its mucosal protective effect. The authors hypothesised that patients using NSAIDs might have a lower risk of developing stomach ulcers if they ate spicy foods containing capsaicin at the same time.

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Pruritus

Patients on chronic haemodialysis frequently have pruritus, however the underlying cause of this symptom remains unknown.In renal failure, pruritus is thought to be transmitted in part through substance P, which is depleted by capsaicin.[14,15] Topical 0.025% capsaicin improved symptoms in 70% of patients compared to a placebo in a double-blind crossover study of 19 individuals on routine haemodialysis. [14] Up to 8 weeks after treatment ended, the antipruritic effect was still noticeable.

Up to 5 percent of the population suffers with pruritus ani, a condition characterised by acute itching in the anus and perianal region. There is often no identifiable cause, and the illness can be challenging to cure.[16-18] One study found that a topical treatment containing 0.006% capsaicin was more effective than menthol at relieving pain in 31 of 44 participants.

Future directions and therapies

Capsaicin and TRPV1 antagonist analogues have been synthesised, and they shed light on the therapeutic potential of these substances in the future. Nociceptive pain in mice was used to prove that the capsaicin analogue SDZ 249-665 has analgesic effects.[19] 61 In an inflammatory pain model using guinea pigs and rats, it also has analgesic properties. Intensity-wise, it was stronger (45 times when given orally, 3 times more if subcutaneous).

SDZ 249-665 has the potential to be more beneficial than capsaicin since it does not cause the same excitatory (bronchoconstriction and blood pressure increases) and pungent effects. One potential benefit over capsaicin is that it can be taken orally as a preparation.

Capsazepine and other potent TRPV1 antagonists show promise as analgesics, especially for inflammatory pain. SC0030, a novel, non-vanilloid TRPV1 antagonist developed by Suh and Oh22, has been shown to have analgesic effects in mice. It had the same efficacy as the painkiller indomethacin.[20-21]

One of the most powerful inflammatory agents, leukotriene B4 (LTB4) contributes to inflammatory pain, activates neutrophils, and causes them to degranulate. In addition, LTB4 may contribute to the emergence of inflammatory hyperalgesia by activating the TRPV1 receptor. Agents that block LTB4 and TRPV1 receptors might be useful in treating inflammatory diseases. Just lately, McHugh62 created molecules that show promise as a starting point for the design of additional useful therapeutics. Many other TRPV1 antagonists are currently being tested for their potential to alleviate pain, asthma symptoms, and urine incontinence.[24-26].

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