Capsaicin : A Review

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Abstract

Capsaicin is the principal pungent component in the fruits of plants from the genus Capsicum. It is unique among naturally occurring irritant compounds because the initial neuronal excitation evoked is followed by a long-lasting refractory period, during which the previously excited neurons are no longer responsive to a broad range of stimuli. This process is referred to as desensitization and has been exploited for its therapeutic potential. The effect of capsaicin on pain is thought to be mediated through its effects on sensory neurons with unmyelinated C-fibers, which participate in the transmission of nociceptive information to the central nervous system and release a number of pro-inflammatory mediators involved in pain pathways. Capsaicin has analgesic and anti-inflammatory properties and has been used in topical creams and gels for treating pain due to various conditions. Adverse effects include local discomfort characterized by burning, stinging and redness of the skin but systemic events are rare. This article discusses the mechanism of action and effects of capsaicin and its therapeutic uses.

Key words: Capsaicin, Pain, Vanilloid, Topical

Introduction

Capsaicin is a chemical irritant that is the active ingredient in hot chilli peppers of the genus capsicum. It is an irritant for mammals, including humans, and produces a sensation of burning in any tissue with which it comes into contact. 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. It is theorized that the name ‘Capsicum’ was derived from the Greek word ‘kapto’ meaning “to bite”, which appropriately describes the main characteristics of the fruit. Capsaicin was first isolated in 1816 in partially purified crystalline form by Bucholz, and in pure crystalline form in 1876 by Thresh, who named it capsaicin.

Capsaicin (trans-8-methyl-N-vanillyl-6-nonenamide) has a molecular formula of C_{18}H_{27}NO_{3}, and in its pure form appears as a hydrophobic, colorless, odorless, crystalline to waxy compound.

Capsaicin and several related compounds are called as Capsaicinoids, and are derived from the dried fruit of plants of the Solanaceae family, produced as secondary metabolites by chilli peppers. Capsaicin is the main capsaicinoid in...
chilli peppers followed by dihydrocapsaicin. Capsaicin and dihydrocapsaicin account for approximately 90% of capsaicinoids in chili pepper fruit, are the two most potent capsaicinoids and their molecules differ only in the saturation of the acyl group. Minor capsaicinoids include nordihydrocapsaicin, homodihydrocapsaicin and homocapsaicin. Besides these natural capsaicinoids, one synthetic member of the capsaicinoid family also exists, namely nonivamide, which is used as a reference point for determining the relative pungency of the other capsaicinoids.

Capsaicin has been studied extensively to exploit its potential therapeutic value and as a means to probe the physiology of pain transmission. It has three characteristic effects – excitation, desensitization and neurotoxicity.

**Pharmacology and Mechanism of Action**

Capsaicin is thought to have selective actions on unmyelinated C-fibers and thinly myelinated A primary sensory neurons. It activates sensory afferent nerve fibers by binding to a receptor called the vanilloid receptor subtype 1 (VR1). VR1 is a member of the superfamily of Transient Receptor Potential (TRP) ion channels, and is also referred to as TRPV1. This TRPV1 receptor is a transmembrane receptor-ion channel complex which provides integrated responses to temperature, pH, and endogenous lipids. 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. When activated, it increases membrane permeability to cations, particularly to calcium and sodium ions.

When capsaicin binds to TRPV1, it causes the channel to open below 37 °C (normal human body temperature), which is why capsaicin is linked to the sensation of heat. Prolonged activation of these neurons by capsaicin depletes presynaptic substance P, one of the body's neurotransmitters for pain and heat. It also alters the release from peripheral terminals of neurokinin A, calcitonin gene-related peptides and other neurotransmitters/neuropeptides involved in inflammatory response. Capsaicin thus mimics a burning sensation, the nerves are overwhelmed by the influx, and are unable to report pain for an extended period of time. With chronic exposure to capsaicin, neurons are depleted of neurotransmitters, leading to reduction in sensation of pain and blockade of neurogenic inflammation. If capsaicin is removed, the neurons recover.
The activation of TRPV1 by capsaicin results in sensory neuronal depolarization, and can induce local sensitization to activation by heat, acidosis, and endogenous agonists as shown in Figure 1. It is now thought that high concentrations of capsaicin or repeated applications can produce a persistent local effect on cutaneous nociceptors, which is described as defunctionalization and includes reduced spontaneous activity and a loss of responsiveness to a wide range of sensory stimuli.3

Capsaicin thus binds to nociceptors in the skin, causing an initial excitation of the neurons and a period of enhanced sensitivity. This is usually perceived as itching, pricking, or burning, with cutaneous vasodilation, and is thought to be due to selective stimulation of afferent C fibres and release of substance P. This is followed by a refractory period with reduced sensitivity and, after repeated applications, persistent desensitisation, possible due to depletion of substance P.9

Uses

Food: Capsaicin is commonly used in food products to give them added spice or "heat" (pungency) because of the burning sensation it causes when it comes in contact with mucous membranes. In high concentrations, capsaicin will also cause a burning effect on other sensitive areas of skin. If left alone, the burning sensation slowly fades away in around 6–8 hours.

Therapeutic Uses

Capsaicin is available as creams, sprays or gels, which may be in various combinations with local anesthetics and analgesics. It is usually used in a dose of 0.025% or 0.075% (cream), applied three-four times daily for 4-8 weeks. Capsaicin is also currently available as an 8% transdermal patch with a longer duration of action (over many weeks).3

- Capsaicin may be used as a cream for the temporary relief of minor aches and pains of muscles and joints (musculo-skeletal pain) associated with arthritis, simple backache, strains and sprains.2
- To relieve the pain of peripheral neuropathy such as post-herpetic neuralgia caused by shingles. It is considerably safer than other regimens employed particularly antidepressants and neuroleptics. Capsaicin avoids problems with drug interactions and systemic toxicity and therefore topical capsaicin has suggested for consideration in the initial management of post-herpetic neuralgia.4

Wagner T, Poole C, Roth-Daniek A (2013)10 found that capsaicin 8% patch produced significant pain reduction in patients with a variety of peripheral neuropathic pain, with an associated significant reduction in prescribed concomitant neuropathic pain medications.

- To reduce or eliminate post-surgery neuropathy caused by various types of surgery and diabetic neuropathy.
- To treat psoriasis as an effective way to reduce itching, scaling and erythema. It has also been used in treating pruritus, and may be used in concentrations of 0.01% and 0.025%.2,9
- Pain in Burning Mouth Syndrome, Guillain-Barre syndrome, refractory pain, cluster headache9, urticaria, rheumatoid arthritis and osteoarthritis4, and atypical odontalgia11.

Petruzzi M, Lauritano D, De Benedittis M et al (2004)12 in a controlled trial used systemic oral capsaicin 0.25% for treating 25 patients with burning mouth syndrome. They found that even though systemic capsaicin was therapeutically effective for the short-term treatment of burning mouth syndrome, there was significant gastric toxicity (gastric pain) which could preclude its long-term use.

Other Effects

Capsaicin has also been thought to be a cancer-suppressing agent. It blocks the translocation of nuclear factor kappa B (NF-B), activator protein 1 (AP-1) and signal transducer and activator of transcription (STAT3) signaling pathway that are required for carcinogenesis. It is also thought to generate reactive oxygen species in cells, with resultant induction of apoptosis and cell cycle arrest, which is beneficial for cancer chemoprevention.1

Capsaicin is helpful in healing and preventing gastric ulcers by stimulating alkali and mucus secretions, and gastric mucosal blood flow.4
Adverse Effects

Adverse events from capsaicin are mainly at the application site (burning, stinging, erythema), and systemic events are rare. The burning and erythema is thought to be worse if applied to moist areas. Inhalation of cream may induce respiratory irritation and bouts of sneezing. Although the presumed lack of toxicity of capsaicin in food does not preclude adverse effects related to its actions on the skin, topical capsaicin is also generally regarded as safe for medical use.

Conclusion

Capsaicin can be a useful topical analgesic to control various pain conditions and may be useful as an adjunct or sole therapy for patients who are unresponsive to, or intolerant of other treatments. Capsaicin is thought to have anti-inflammatory, anti-oxidant, anti-proliferative and anti-cancer potential and thus have a chemopreventive effect against a number of chronic inflammatory diseases, including cancer. Topical capsaicin has been used in treating neuropathic pain, post-herpetic neuralgia, pain in musculoskeletal disorders and burning mouth syndrome. Topical capsaicin is poorly absorbed transdermally in humans and therefore has almost no systemic adverse effects. While burning and stinging at the site of application have been reported, they usually resolve spontaneously after few applications. Capsaicin may thus be useful as adjunctive therapy in various pain conditions or as sole treatment in patients who are unresponsive to other commonly used modalities of treatment.

References