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Review

Mechanisms and clinical uses of capsaicin ☆

Surinder Kumar Sharma [a], Amarjit Singh Vij [b], Mohit Sharma [c,*]

[a] Department of Biochemistry, Punjab Institute of Medical Sciences, Jalandhar, India
[b] Department of Medicine, Punjab Institute of Medical Sciences, Jalandhar, India
[c] Department of Neurology, State University of New York (SUNY) Downstate Medical Center and Kings County Hospital Center, 450 Clarkson Avenue, Box 1228, Brooklyn, NY 11203-2098, United States

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ABSTRACT

Capsaicin is the active ingredient of chili peppers and gives them the characteristic pungent flavor. Understanding the actions of capsaicin led to the discovery of its receptor, transient receptor potential vanilloid subfamily member 1 (TRPV1). This receptor is found on key sensory afferents, and so the use of capsaicin to selectively activate pain afferents has been studied in animal and human models for various indications. Capsaicin is unique among naturally occurring irritant compounds because the initial neuronal excitation evoked by it 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 known as defunctionalisation has been exploited for therapeutic use of capsaicin in various painful conditions. We reviewed different studies on mechanisms of action of capsaicin and its utility in different clinical conditions. A beneficial role of capsaicin has been reported in obesity, cardiovascular and gastrointestinal conditions, various cancers, neurogenic bladder, and dermatologic conditions. Various theories have been put forth to explain these effects. Interestingly many of these pharmacological actions are TRPV1 independent. This review is aimed at providing an overview of these mechanisms and to also present literature which contradicts the proposed beneficial effects of capsaicin. Most of the literature comes from animal studies and since many of these mechanisms are poorly understood, more investigation is required in human subjects.

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1. Introduction

Capsaicin is the active ingredient of chili peppers obtained from the plants of genus *Capsicum*, the most heavily consumed chili in the world. Capsaicin and related compounds form a naturally occurring chemical group called capsaicinoids. Capsaicin gives the characteristic pungent flavor to chilies and is believed that these

☆Chemical compounds studied in the article: capsaicin (PubChem CID: 1548943); substance P (PubChem CID: 36511); resiniferatoxin (PubChem CID: 6324660); ALGRX 4975 (PubChem CID: 57369257); zucapsaicin (PubChem CID: 1548942); capsiate (PubChem CID: 9839519); dihydrocapsiate (PubChem CID: 9873754); and nordihydrocapsiate (PubChem CID: 9817607).

* Corresponding author. Tel.: +1 718 245 4790; fax: +1 718 245 4799.
E-mail address: mohitsharma.dr@gmail.com (M. Sharma).

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chemicals are produced by the plant as a natural defense against herbivores and fungi. The effects of capsaicin on human body have been studied for more than a century. Hogyes in 1878 observed the burning sensation and hyperemia produced by an extract of *Capsicum* when applied on human skin (Toh et al., 1955). Later numerous animal studies revealed a fall in blood pressure, increase in salivary and gastric secretion and increased intestinal activity after an intravenous injection of *Capsicum* extract (de Lille and Ramirez, 1935; Nast, 1923). As a result, capsaicin has been an exciting pharmacological agent and its utility in different clinical conditions is being explored.

We aim to provide a review of the pharmacological properties of capsaicin and the mechanisms behind it. We identified references for this review by searching MEDLINE, EMBASE and CINAHL electronic databases through August, 2013. Keywords and MeSH terms like “capsaicin”, “clinical uses”, “pain”, “obesity”, and “transient receptor potential vanilloid subfamily member 1” were used. We also hand searched related articles in these electronic databases. To make the review comprehensive, we considered articles published in non-english language as well. The reference list was compiled based on their relevance to the broad scope of this review.

2. Chemistry of capsaicin molecule

Capsaicin (*trans*-8-methyl-*N*-vanillyl-6-nonenamide) is a naturally occurring alkaloid derived from plants of the genus *Capsicum*, better known as chili pepper fruit. The molecular formula for capsaicin is $C_{18}H_{27}NO_3$. It is a highly volatile, pungent, hydrophobic, colorless and odorless white crystalline powder. It is synthesized in the chili pepper by addition of a branched-chain fatty acid to vanillylamine (Fujiwake et al., 1980). Commercially it is manufactured by the reaction of vanillylamine with 7-methyloct-5-ene-1-carboxylic acid chloride or isolated from paparika or obtained by grinding dried ripe fruits of *Capsicum frutescens L.* (chili peppers) into a fine powder. The formulation types registered are dry powder, liquid formulation and liquid spray ground. Capsaicin is believed to be metabolized by dehydrogenation, producing unique macrocyclic, -diene, and -imide metabolites. The metabolism was shown to be catalyzed by enzymes cytochrome P 1A1, 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4 (Reilly et al., 2003).

3. Pharmacological actions of capsaicin

3.1. Pain relief

Transient receptor potential vanilloid 1 receptor (TRPV1), also known as the capsaicin receptor, is part of the transient release potential (TRP) ion channel family which helps the body in sensing heat or warmness (Ramsey et al., 2006). After its cloning in the year 1997 from a rat dorsal root ganglia, TRPV1 was investigated for a rather widespread distribution in rat and human brain. Mezey et al. (2000) performed immunocytochemistry and in situ hybridization histochemistry using specific ribonucleic acid (RNA) probe to localize TRPV1 expressing cells in the rat brain, later confirmed by reverse transcription-polymerase chain reaction (RT-PCR). RT-PCR verified the expression of TRPV1 messenger RNA in rat cortex, hippocampus, and hypothalamus. This was followed by numerous investigators detecting TRPV1 expression in the cortex, hippocampus, dentate gyrus, central amygdala, striatum, hypothalamus, thalamus, cerebellum, locus ceruleus, cochlear nuclei, nucleus of the trigeminal nerve and inferior olive (Cristino et al., 2006; Starowicz et al., 2008).

Evidence of TRPV1 involvement in pain perception was presented by Giordano et al. (2012) who showed that the prelimbic and infralimbic cortex undergoes several changes following neuropathic pain, including enhanced TRPV1 expression on glutamatergic fibers and excitatory signaling by basolateral amygdala-medial prefrontal cortex (mPFC) neurons, with subsequently increased extracellular levels of glutamate. This contributes to the processing of noxious stimuli. Furthermore, N-arachidonoyl-serotonin, which is a hybrid TRPV1 antagonist and fatty acid amide hydrolase inhibitor, normalized the imbalance between excitatory and inhibitory responses in the mPFC neurons, resulting in pain inhibition (de Novellis et al., 2011). Capsaicin is an agonist of TRPV1 and reduces its heat activation threshold (Knotkova et al., 2008). TRPV1 is activated via phosphorylation by protein kinases, the calcium and calmodulin-dependent protein kinase II (CaMK II kinase) and cleavage of phosphatidylinositol 4,5-bisphosphate (PIP2) by phospholipase C (Mohapatra and Nau, 2003; Premkumar and Ahern, 2000; Vellani et al., 2001). The N-terminus of TRPV1 has several phosphorylation sites for protein kinases which aid in its activation (Caterina et al., 1997) whereas TRPV1 desensitization results from its dephosphorylation by phosphatises (Ma and Quirion, 2007). Capsaicin activated TRPV1 goes into a long refractory state and thus a previously excited neuron is resistant to various stimuli ranging from mechanical pressure to endo/exogenous pain and proinflammatory agents (Szallasi and Blumberg, 1999). At the molecular level, this results from extracellular calcium dependent conformational changes in the receptor protein, ultimately closing the channel pore (Liu and Simon, 1996). However, this effect may be temporary and therefore may not account for a persistent pain relief seen clinically.

Upon excitation, TRPV1 releases sensory neuropeptides, which are dependent on capsaicin concentration used (JM, 1996) but then also prevent the restoration of the neuropeptides by blocking axoplasmic transport of substance P and somatostatin in sensory neurons (Gamse et al., 1982), thereby depleting neuropeptides. This was thought to be primarily responsible for pain relief, but capsaicin appears to provide analgesia by a cascade of events resulting in “defunctionalization” of the nociceptive fibers rather than just by depleting the neuropeptides (Anand and Bley, 2011). Defunctionalization may include loss of membrane potential, depletion of neuropeptides, inability to transport neurotrophic factors, and reversible retraction of epidermal and dermal nerve fiber terminals (Anand and Bley, 2011). Calcium overload may result in a loss of mitochondrial function and inhibition of metabolism may disrupt the plasma membrane integrity, causing the nerve ending to collapse (Anand and Bley, 2011). Therefore, defunctionalization of the afferent neurons by stimulation of TRPV1 causes long term functional and phenotypic alterations in the whole neuron.

While capsaicin has been shown to damage the sensory nerve endings (Anon, 2007; Chard et al., 1995), repeated topical application of capsaicin also results in degeneration of the cutaneous autonomic nerve fibers, decreasing the pain sensation (Nolano et al., 1999; Simone and Ochoa, 1991). Although not clearly understood but TRPV1 mediated calcium influx and glutamate release have been thought to be responsible for it (Sikand and Premkumar, 2007). Resiniferatoxin (RTX), a potent analog of capsaicin, has been shown to cause loss of unmyelinated nerve fibers and detectable levels of damage to myelinated ones as well in adult rats, showing that RTX reduces thermal pain perception by depleting neurons that express TRPV1 (Pan et al., 2003).

For pain relief, capsaicin has been approved by the US Food and Drug Administration as an 8% dermal patch. Each patch has synthetic capsaicin 640 mcg/cm^2 with total dose of 179 mg in one patch (Qutenza, 2013). A low dose application (0.075% cream and 0.025% gel) has shown no clinical use in pain reduction (Derry and Moore, 2012; Kulkantrakorn et al., 2013). There have been