inflammatory mediators such as bradykinin and the activity of TRPV1 is modulated by certain sensitizes its responses to other stimuli [26, 41].

Moreover, TRPV1 is able to respond to a multiplicity of stimuli by modulating its activity [8, 18].

Besides capsaicin, TRPV1 is activated by noxious heat (> 43°C), low pH (< 5.2) as well as other exogenous and endogenous activators [8, 18].

TRPV1 is a ligand-gated, nonselective cation channel with a high permeability for Ca^{2+} [9].

Capsaicin is a highly selective agonist for TRPV1 (transient receptor potential cation channel, subfamily V, member 1) receptor. In the skin, the capsaicin receptor is present in nociceptive nerve fibres and non-neural structures and its activation has a biphasic effect with an excitatory initial phase, followed by a persistent refractory state known as desensitisation, suggesting the possibility of using capsaicin as a therapeutic agent in chronic pain syndromes and in chronic inflammatory skin diseases. Investigation of cutaneous physiological and pharmacological mechanisms of action of capsaicin may lead to identifying new therapeutic targets and new diagnostic methods useful in clinical practice.

Keywords: capsaicin, transient receptor potential cation channel subfamily V member 1 (TRPV1), neurogenic inflammation, pain prostanoids, bradykinin, substance P, calcitonin gene-related peptide (CGRP) [31] and plays a key role as

Capsaicin receptor expression and roles

The capsaicin receptor TRPV1 is present in various structures of the nervous system and other organs and tissues, and is involved in different physiological and pathophysiological processes depending on its location [26, 42].

TRPV1 is highly expressed in the small diameter dorsal root ganglion (DRG) neurons which give rise to unmyelinated type C nerve fibres [22], but is also present in the thin myelinated A-delta fibres [24].

In the peripheral endings of primary sensory neurons TRPV1 is co-localised with neuropeptides, such as substance P (SP) and calcitonin gene-related peptide (CGRP) [31] and plays a key role as

Abstract

Capsaicin is a highly selective agonist for TRPV1 (transient receptor potential cation channel subfamily V member 1) receptor. In the skin, the capsaicin receptor is present in nociceptive fibres and non-neural structures and its activation has a biphasic effect with an excitatory initial phase, followed by a persistent refractory state known as desensitisation, suggesting the possibility of using capsaicin as a therapeutic agent in chronic pain syndromes and in chronic inflammatory skin diseases. Investigation of cutaneous physiological and pharmacological mechanisms of action of capsaicin may lead to identifying new therapeutic targets and new diagnostic methods useful in clinical practice.

Rezumat

Capsaicina este un agonist cu selectivitate ridicată pentru receptorul TRPV1. La nivel tegumentar, receptorul pentru capsaicină este prezent la nivelul fibrelor nervoase nociceptive și în structurile non-neurale, iar activarea sa determină un efect bifazic, cuprinzând o etapă inițială excitatorie urmată de o stare refractară persistentă numită desensibilizare, sugerând astfel posibilitatea utilizării capsaicinei ca agent terapeutic în sindroamele dureroase cronice și la bolile inflamatorii cronice cutanate. Investigarea mecanismelor fiziologice și farmacologice de acțiune a capsaicinei la nivel cutanat pot conduce la identificarea unor noi ținte terapeutice și unor noi metode diagnostice utile în practica clinică.

Keywords: capsaicin, transient receptor potential cation channel subfamily V member 1 (TRPV1), neurogenic inflammation, pain prostanoids, bradykinin, substance P, calcitonin gene-related peptide (CGRP) [31] and plays a key role as

Introduction

Capsaicin (trans-8-methyl-N-vanillyl-6-nonenamide) is the major pungent ingredient of hot pepper fruit (Capsicum annuum) and is a highly selective agonist for the transient receptor potential cation channel subfamily V member 1 (TRPV1) [26]. TRPV1 is a ligand-gated, nonselective cation channel with a high permeability for Ca^{2+} [9]. Besides capsaicin, TRPV1 is activated by noxious heat (> 43°C), low pH (< 5.2) as well as other exogenous and endogenous activators [8, 18]. Moreover, TRPV1 is able to respond to a multiplicity of stimuli by modulating its activity [26, 41, 43]. Thus, heat and slightly acidic pH sensitize its responses to other stimuli [9, 40]. Also, the activity of TRPV1 is modulated by certain inflammatory mediators such as bradykinin and prostaglandins, probably by phosphorylation of the receptor mediated by protein kinase A (PKA) or protein kinase C (PKC) [29].

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a molecular integrator of various physical and chemical noxious stimuli, being involved in nociception, inflammatory pain and neurogenic inflammation [8, 40, 21].

In the skin, TRPV1 is expressed both by neural and non-neural structures. The capsaicin receptor is present in cutaneous sensory nerve fibres, epidermal keratinocytes, mast cells, skin blood vessels, hair follicles, sebocytes and eccrine sweat glands [19, 36].

TRPV1 may function as an extra-neuronal receptor [31], activation by capsaicin inducing a calcium influx in the epidermal keratinocytes [34, 35]. As well, TRPV1 activation induces an increased expression and synthesis of pro-inflammatory factors and keratinocytes may have an active role in the inflammatory response arising from cutaneous noxious stimulation [35].

### Skin reactions induced by capsaicin

Capsaicin has a biphasic effect on the primary sensory neurons with an excitatory initial phase, followed by a persistent refractory state known as desensitisation [38]. Depending on the time of action and concentration, capsaicin can also induce neurotoxicity [17].

Initially, capsaicin activation of TRPV1 on nociceptive nerve endings leads to the transmission of nociceptive signals to the central nervous system inducing a burning sensation. Further, after activation of capsaicin-sensitive sensory nerve endings various neuropeptides, such as SP and CGRP are released [16, 30] thus, being triggered a transient local inflammatory reaction called neurogenic inflammation.

The initial events caused by capsaicin are followed by allodynia and hyperesthesia / hyperalgesia to mechanical and heat stimuli [14, 23, 33].

By repeated administration of capsaicin, these effects are followed by a reversible defunctionalisation of nociceptive sensory nerve fibres [2], characterized by a decrease of the local pain and a reduction of hyperesthesia to mechanical and heat stimuli [23] suggesting the possibility of using capsaicin as a peripheral analgesic in chronic pain syndromes [6, 13]. Moreover, neurogenic inflammation is minimized by the previous capsaicin treatment, suggesting a potential therapeutic role in chronic inflammatory skin diseases [37].

### Safety and efficacy in clinical application of capsaicin

By depletion of SP, when administered topically, capsaicin has shown some promise in the treatment of psoriatic disorder, pain induced by musculoskeletal disorders and neuropathic pain as well as of post herpetic neuralgia. Topical use of capsaicin is valuable because it avoids the interaction with other drugs as well as systemic toxicity. In addition, topical therapy is reported mainly accompanied by such adverse effects as stinging and burning sensations at the application site, usually solved by themselves after no more than a few repeated applications. In spite of its observed usefulness in that respect, only a limited number of studies have been conducted with systemic capsaicin. As it is, capsaicin was developed as a medicinal product meant for initial treatment of various diseases.

### Capsaicin: dermal toxicity

With a reported dermal lethal dose 50% (LD50) level of > 512 mg/kg body weight as determined in mice, capsaicin is considered highly irritant in humans, the respective exposure generating stinging or burning sensations. In cases of pre-existing dermatitis or longer-term exposure, rashes and blistering have also been reported. If exposed, mouse ears develop oedema after one hour of application time [20, 32].

As proof of dermal toxicity in humans, we can mention the reported cases of workers handling peppers, who developed a form of contact dermatitis also known as the "Hunan hand" [44]. If used topically on the tongue or smooth skin, such as the lips, capsaicin application results in a form of burning pain, whose intensity directly relates to the extent of capsaicin-induced increase of the temperature and blood flow [4, 5].

### Capsaicin: uses and outcomes

**Capsaicin and neuropathic pain**

Analgesics for oral use are significantly accompanied by adverse reactions and their efficacy is also lower. Therefore, topical use of analgesics has been considered, allowing direct application in the painful area and correspondingly diminishing the potential for occurrence of systemic adverse reactions, which is an added advantage.

In the case of capsaicin, the therapeutic strategy of its topical application involves desensitization of sensory C-fibre neurons and TRPV1 vanilloid receptor [3, 15].

As found in the treatment of certain neuropathic conditions and more specifically in the therapy of post-herpetic neuralgia [27], low doses of capsaicin have demonstrated a quite diminished efficacy, whereas the optimum currently available data have been found in topical 8% capsaicin.

In spite of the relatively limited surplus number of patients, in which benefits could be observed in studies conducted comparing capsaicin treatment with a control group, there have been additional gains accompanying actual high levels of pain relief, pertaining to the quality of life area, such as
diminished feelings of depression and fatigue as well as improved sleep. That is why, the efficacy of higher concentrations of topical capsaicin, have been considered similar to other chronic pain therapies. However, because of the relative expensiveness of applications, both single and repeated, it is likely on one hand that topical capsaicin in higher concentrations to be used in case of failure of other existing therapies, and, on the other, that the repeated use not to be advisable unless pain relief is substantially documented. In case of repeated and longer-term application, even with established efficacy, occurrence of unknown risks is also possible; mainly so, on the level of epidermal innervation [11, 39].

Two independently performed meta-analyses [2] have confirmed the clinical efficacy, in the treatment of post herpetic neuralgia and HIV distal sensory polyneuropathy of the 8% capsaicin topical administration. In addition, a dermal patch has also been developed, having an adhesive layer that contains synthetic pure trans-capsaicin in high concentrations (8% w/w) [15, 26]. In relation to this capsaicin patch, all patients have demonstrated very low systemic absorption after 60-90 minutes application, whereas the maximum plasma concentration values were 17.8 ng/mL [4]. In the context of additional reporting of certain adverse reactions, the effectiveness of capsaicin for pain relief remains highly debated. Conflicting results have also been recorded after basic and epidemiological research, indicating the potential role of capsaicin in either causing or preventing skin cancer [4]. In that respect, one hypothesis holds the non-carcinogenetic potential of capsaicin in itself, in the absence of a tumour promoting factor, as shown by experimental topical application to mice dorsal skin, when no cancer developed. Conflictingly however, results also appear to indicate that complete TRPV1 blockade for the purpose of pain relief as well as long-term, chronic topical capsaicin application possibly increases the risk for skin cancer occurrence, even more if tumour promoters such as sunlight are present [4].

Topical application of capsaicin in the treatment of rheumatic diseases

In rheumatic diseases, the pathogenesis of pain and inflammation involves the action of SP. Therefore, as a SP depletory, capsaicin has been considered for osteoarthritis and rheumatoid arthritis pain therapy. A randomized, double-blind trial has been conducted in that respect, enrolling 31 patients with rheumatoid arthritis and 70 patients with osteoarthritis, who were instructed to treat their painful knees with applications of 0.025% capsaicin cream (52 patients) or placebo (the capsaicin cream vehicle) (49 patients), four times every day for 4 weeks. For as much as 80% of the respective capsaicin-treated patients, alleviation of pain occurred after 2 weeks of treatment. As reported by approximately 44% (23 patients) of the 52 capsaicin-treated patients, the major adverse effect encountered was a temporary burning sensation experienced at the application site. Therefore, capsaicin cream has been rated as an effective and safe treatment in some rheumatic diseases pain [10].

Use of capsaicin in the treatment of psoriasis vulgaris

A double-blind clinical trial has been designed to study the outcomes of topical capsaicin, as substance with known potential to inhibit cutaneous vasodilatation, on moderate to severe forms of psoriasis. The main characteristic of the patients enrolled was that they displayed symmetrically distributed psoriasis lesions, which allowed topical application of capsaicin to the psoriatic lesion site on one side, whereas on the twin psoriatic lesion on the other side of their body, an identically looking vehicle was applied. The research was developed over a 6 weeks period, with mid-term (3 weeks of treatment) and end of term (6 weeks of treatment) assessment of potential alleviation of erythema and scaling and global psoriasis improvement. The final results of the study showed considerable overall improvement in the capsaicin treated sites as compared with the placebo treated sites. Approximately half of the patients reported itching, stinging and burning sensations accompanied by redness of the skin at the capsaicin site on first application, diminishing or even entirely vanishing on further applications.

Outcomes for effectiveness and the reported comparatively slight adverse reactions uphold the usefulness of topical capsaicin treatment as a new approach in psoriasis therapy [1]. Capsaicin creams have been developed with proven effectiveness in alleviating inflammation and itching.

Use of capsaicin in the treatment of pruritic psoriasis

In addition to its role in the pathogenesis of pain and inflammation, SP is also involved in psoriasis and pruritus pathophysiology. Due to the same properties as powerful SP depletory, topical capsaicin has been the object of a trial conducted in patients with pruritic psoriasis, which revealed its effectiveness as a pruritic psoriasis therapy [12].

Topical capsaicin – a diagnostic tool

During the last years, a new field of investigation has been opened for the clinical applications of topical capsaicin in the diagnosis of various diseases. A recent study used applications of capsaicin micro-emulsions in obstructive pulmonary disease
diagnostic [28]. A previous research of our group showed that in vivo reflectance confocal microscopy (RCM) allows the investigation of dermal micro-vessels and can be used for the assessment of skin neurogenic vasodilator reaction induced by capsaicin [7, 25]. Our results suggest that RCM evaluation of skin neurogenic inflammation induced by capsaicin could be useful for the investigation of thin cutaneous nerve fibres functionality.

Conclusions

Investigation of cutaneous physiological and pharmacological mechanisms of action of capsaicin may lead to identifying new therapeutic targets and new diagnostic methods useful in clinical practice.

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