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Review

Research progress of capsaicin responses to various pharmacological challenges

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ABSTRACT

Capsaicin, a well known vanilloid, has shown evidence of an ample variety of biological effects which make it the target of extensive research ever since its identification. In spite of the fact that capsaicin causes health hazards in quite a few ways, yet, the verity cannot be ignored that capsaicin has several therapeutic implications. In patients with hypersensitive bladders, vesical instillation of 1 mM capsaicin markedly improved urinary frequency and urge incontinence. Again, administration of capsaicin favors an augmentation in lipid mobilization and a decrease in adipose tissue mass. Topical capsaicin cream as well decreases postsurgical neuropathic pain and is preferred by patients over a placebo among other therapies. Several in vitro studies have revealed that capsaicin results in growth arrest in some transformed cell lines. Furthermore, capsaicin has been proven to be an undeniably exciting molecule and remains a valuable drug for alleviating pain and itch. It has been recognized that capsaicinoids are the most potential agonists of capsaicin receptor (TRPV1). However, vanilloids could exert the beneficial effects not only through the receptor-dependent pathway but also through the receptor-independent one. The involvement of serotonin, neuropeptide Substance P and somatostatin in the pharmacological actions of capsaicin has been expansively investigated. Better understanding of the established TRPV1 receptor mechanism as well as exploring other possible receptor mechanism may publicize other new clinical efficacies of capsaicin. Further, clinical studies are required in several of these conditions to establish the efficacy of capsaicin.

1. Introduction

Natural products continue to be the most successful source of drug leads providing opportunities to study important biology. Capsaicin is a compound found in chili peppers, responsible for their burning and irritant consequences. This dynamic ingredient in hot pepper was first isolated more than 100 years ago. Despite this early breakthrough, it was not until 1923, that the definite chemical structure of capsaicin was determined [1] and finally in 1930, capsaicin was chemically synthesized by Spath and Darling [2]. The chemical structure of capsaicin consists of a benzene ring and a long hydrophobic carbon tail with a polar amide group. In 1961, Japanese chemists S. Kosuge and Y. Inagaki, isolated substances from chilli pepper, analogous to capsaicin and nomenclature as capsaicinoids. The most active capsaicinoids are dihydrocapsaicinoid, nordihydrocapsaicinoids, and homocapsaicin in the content 22%, 7% and 1% respectively [3]. Capsaicinoids contain approximately 30% of the total capsaicinoids mixture and are mostly responsible for the pungency of capsaicin [4]. Nevertheless, the definite percentage of capsaicin and other capsaicinoids varies depending on the pepper source and extraction procedure [5]. Capsaicin has shown evidence of a wide variety of biological effects which make it the target of extensive research since its early identification [6]. Presently, capsaicin is in Phase III clinical trials as an agent for treating rheumatoid arthritis, postoperative pain, acute/chronic neuropathic and musculoskeletal pain [7].

Even though commonly used, the strong pungency confines the use of a large amount of capsaicin in daily food and medicine. Pertaining to the toxicity of capsaicin in capsicum fruits, some investigators reported in the following ways: Nagabhushan and Bhide demonstrated capsaicin to be mutagenic confirmed by micronucleus as well as Ames test [8]. Data of various animal studies and case control reports suspected capsaicinoids to be a risk factor for duodenal [9], stomach, liver [10], gastric [11] and gallbladder cancer [12]. However, experiments are on track to modify the capsaicin molecule to overcome some of the adverse

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effects. Quite a few case reports have also described adverse respiratory effects and death in humans following exposures to concentrated capsaicinoid aerosol formulation [13,14,15]. In further scientific terms, capsicum is pungent, affects thermoregulation, triggers autonomic reflexes, and is scantily absorbed. Exploitation of all these properties of capsicum lead to the development of pepper spray, a suitable candidate to foil uncontrolled rioting and nab contrary suspects by law enforcement officers [16,17] and as a self-defense weaponry by women [18].

Despite its unfavorable effects, capsaicin has been utilized for a wide variety of clinical conditions. Clinical investigations of topical capsaicin include assessment in chronic pain syndromes *viz*. rheumatoid arthritis, postherpetic neuralgia, hemodialysis-associated itching, reflex sympathetic dystrophy syndrome, diabetic neuropathy, psoriasis, vulvar vestibulitis and post mastectomy neuroma [19]. It has also been recommended as a treatment for diverse painful syndromes since repeated topical application of capsaicin specifically causes release and prevention, the re-accretion of neuropeptides in unmyelinated, polymodal C-type as well as small myelinated A-delta-type cutaneous nerves. Although capsaicin has been demonstrated to be mutagenic [8], however, topical studies with high-purity capsaicin and standardized protocols suggest substantiation that the genotoxic and carcinogenic potential of capsaicin is quite low and that the purity of capsaicin is imperative [20]. Capsaicin has also shown promising results in preliminary studies for blepharo spasm, prostatic cancer, lung cancer, and various other forms of leukemias [21]. Despite the fact that capsaicin causes health hazards in several ways, however, the verity cannot be ignored that capsaicin has several therapeutic implications as well but these implications, in other indications, has limited applicability because of some conflicting data. For instance, capsaicin has been reported to possess chemopreventive and chemotherapeutic properties [22,23], and moreover, in vivo studies prop up the anti tumorigenic potential of capsaicin [24]. Taken as a whole, capsaicin is a promising drug candidate and may develop subsequently as a initial treatment therapy for a number of diseases. Here, we aim to endow with an up-to-date and comprehensive review of medicinal and pharmacological benefits of capsaicin in diverse health conditions.

2. Preclinical and clinical effect of capsaicin on various organs

2.1. Ocular

Ocular exposure to capsaicin can result in evocation of antidromic stimulation of the trigeminal nerve leading to chemosis and conjunctivitis [25,26]. Necessary treatment involves copious irrigation and use of oral analgesics and topical ophthalmic anesthetics for pain control [27]. Tachykinin-mediated neurogenic slow contraction of the isolated iris sphincter muscle of the rat, pig rabbit and human ciliary muscle are also mediated by cerebrospinal (CS) afferents [28,29,30]. Reports of a randomized case study suggested that visual acuity remained unaffected with exposure to pepper spray [31]. In another case study, it was found that 3 weeks after direct exposure to pepper spray, a significant conjunctivital proliferation was found at the limbus of a 2.5 year old boy. It was hypothesized that the young age of the patient may be an important factor for the severe conjunctivital proliferation in comparison to a mainly uncomplicated course of pepper spray injuries in most adults [32].

2.2. Cardiovascular

According to Toh et al. capsaicin leads to sensitization of baroreceptors in the carotid sinus wall and in the pulmonary vessels [33,34] resulting in a reflex fall in systemic blood pressure and in reduction in the heart rate. In vivo experiments performed on dogs clarified that capsaicin caused a sustained increase in the tension of spiral strips of proximal and distal renal arteries and distal mesenteric arteries of the dog [35]. Furthermore, these findings suggest that capsaicin causes hypertension in dogs by its action on peripheral vasculatures but not on the heart: capsaicin induced vasoconstriction is related intimately to extracellular calcium but not to an adrenergic mechanism. Release of neurotransmitters is generally considered to require the presence of extracellular Ca^{2+} [36,37]. Capsaicin evokes an influx of extracellular Ca^{2+} [38,39] possibly because of its peptide-releasing properties. In ex vivo experiments with whole heart preparations, capsaicin-perfusion caused a concentration-dependent increase in heart rate and calcitonin gene-related peptide (CGRP)-like immunoreactivity (LI) release in combination with a decrease in contractile tension [40]. Experiments performed in the guinea-pig perfused heart, suggest that the effects of capsaicin on peptide release are Ca^{2+} dependent [41]. Moreover, categorization with high performance liquid chromatography (HPLC) of the CGRP-LI released by capsaicin revealed a similar elution position as the CGRP-LI present in extracts of the guinea-pig heart. The HPLC system used, however, does not allow any further conclusion about the nature of CGRP-LI in the guinea-pig heart with regard to α or β forms.

2.3. Pulmonary

Capsaicin was described to exert its respiratory effects partially through the superior laryngeal nerves in the guinea pig and rat [42,43]. Moreover, it is established that doses of capsaicin in μg per kg body weight (b.w) basically stimulate the smallest chemosensitive C-fibres in rodents and guinea pig [44]. Enhanced transfer from vagal C-fibres was shown to instigate a reflex that increases breathing frequency and decreases tidal volume [45]. Capsaicin has shown to increase mean inspiratory flow in studies comparing the effect of capsaicin (10^{-7} M, 0.03 g/m^3) in nebulized dosage form to diluten unaided on the breathing pattern [46]. In another experiment, it was found that capsaicin at the dose of 5 μg/kg induced immediate expiratory apnoea followed by stimulated breathing of increased tidal volume and respiratory rate [47]. Even though the specific role of Substance P (SP) in respiratory rhythm regulation is not clearly known, however, it was found that exogenously applied SP augments respiratory activity in vivo [48] and in vitro [49,50,51]. Medullary slices of neonatal rat generated respiratory-related rhythm, and capsaicin, dose dependently, caused termination of respiratory rhythm time accompanied by SP depletion and increased glutamate release. The effect of depletion of SP by capsaicin slows down gradually and ultimately stops the respiratory rhythmic motor output in the medullary slices and it was proposed that this might occur within the PreBotzinger complex, which involves neurokinin 1 receptor (NK1R) and glutamate receptor. The vanilloid receptor-related transient receptor potential (TRPV) receptors on target cells were found to be the partial mediators for the cytotoxic effects of capsaicin [52]. Therefore, expression of TRPV receptors on lung tissue would be an imperative determinant in the cytotoxic activity of capsaicin in lung cells. Studies have revealed that capsaicin causes apoptosis in human lung adenocarcinoma cells (H460) in a TRPV-independent manner, by regulating enzymes involved in mitochondrial respiration [53].

2.4. Hepatic

Evidence from a rat intestinal ex vivo study envisages that the capsaicin molecule gets readily absorbed from the intestinal tract [54]. As a result, capsaicin ingested from food is probably well absorbed and subjected to considerable first-pass hepatic metabolism. Early studies established the fact that the majority of capsaicin undergoes hepatic metabolization [55]. Several laboratories investigated the in vitro metabolism of capsaicinoids in liver using S9 fractions and hepatic microsomes [56]. Chanda et al. observed that capsaicin was entirely metabolized in rat and human microsomes within 20 min period [57]. Several enzymes may play some role in hepatic drug metabolism, although, cytochrome P450 enzymes are quantitatively by far the most important accounting for many drug-drug interactions. Moreover,