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Review Article:

Is Capsaicin a Pain Inducer or Killer? A Review of its Related Mechanisms

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Abstract

Background: Capsaicin is the chemical responsible for the hot and irritating characteristics of chili peppers. Because it produces both heat and pain, this phytochemical is a valuable means of scientific investment for pain research. **Aim:** This study examines the processes underlying capsaicin-induced pain, emphasizing its importance in understanding brain pain modulation. It also highlights the therapeutic uses of capsaicin in pain management and its analgesic characteristics. Moreover, the major objective is to better understand the dual role of capsaicin as both a pain inducer and a pain killer. **Method:** The authors gathered data from several published studies abstracted from many indexing platforms, including Scopus, Web of Science, Google Scholar, and PubMed, between 2015 and 2024. Results: The findings demonstrate that capsaicin initially functions as a pain stimulant but, with extended application, becomes an excellent analgesic. **Conclusion:** Given its active role in pain regulation, it can regard capsaicin as an intriguing model to potentially understand the molecular mechanism behind pain induction and relief.

1. Introduction

Chilli peppers contain a substance called capsaicin (CAP), which gives them their spicy and irritating properties. This phytochemical is a useful tool in the study of pain since it causes pain in addition to the feeling of heat (1). Even if modern techniques have allowed us to understand pain mechanisms much better, experimental models are still vital and frequently employed. In this regard, CAP is a vital experimental method for examining pain pathways and creating new analgesics, making it one of the most important sources of data in the study of pain (2). Several recent studies have objectively confirmed the analgesic effects of CAP, which several civilizations have long believed to exist (3). Opioids, which are known to cause hyperalgesia despite their recognized therapeutic use as analgesics, also exhibit this paradox (4).

The complex responses elicited by CAP and its therapeutic advantages underscore the necessity of comprehending its mechanisms of action in pain modulation. This review highlights the importance of CAP in improving our present understanding of how the brain modulates pain and examines various pathways of CAP-induced pain. The focus will be on the analgesic characteristics of capsaicin CAP and its clinical application in pain management (5).

The objective of this study is to investigate the complex role of CAP, a compound found in chili peppers, in pain induction and relief. While this phytochemical is well-known for its ability to stimulate pain through its action on pain receptors, it also has analgesic properties when used over time. This research aims to explore the underlying mechanisms of CAP-induced pain and its impact on brain pain modulation. Ultimately, the objective is to use this plant product as a model to better understand the molecular processes behind both pain generation and pain relief, with potential therapeutic implications for pain management.

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2. Method

The researchers performed a comprehensive assessment of the literature to investigate the mechanisms of CAP-induced pain and its therapeutic potential. The data were obtained from various academic databases, including Scopus, Web of Science, Google Scholar, and PubMed, encompassing papers published from 2015 to 2024. The selection procedure entailed locating peer-reviewed articles and research papers that particularly examined the effects of CAP on pain pathways, brain pain modulation, and its dual function as both a pain inducer and an analgesic. The study investigated pertinent facts on CAP's interaction with pain receptors, specifically the TRPA1 channel, its efficacy in alleviating neuropathic pain, and its overall impact on pain perception.

3. CAP

The major component of chilli peppers is capsaicin. Recent investigations indicate that capsaicin possesses dual properties. It exhibits potential biological activities at low doses, although it tends to induce deleterious consequences at elevated concentrations. Capsaicinoids are the primary source of the spicy flavors in chilli peppers, with capsaicin comprising around 69% of the capsaicinoids, regarded as the principal pungent component. The concentration of capsaicin significantly differs among various chilli peppers, leading to variations in the fruit's pungency (6).

3.1. CAP as a phytochemical

Chilli peppers contain CAP (8-methyl-N-vanillyl-6-nonenamide), a phenolic molecule responsible for their unique flavor and spiciness. All Capsicum species, with the exception of Capsicum annuum, produce variable quantities of CAP, and people have utilized these plants as spices for over 6,000 years (7,8). This phytochemical constitutes up to 1% of the mass of chilli peppers and, in conjunction with salt, ranks among the most often utilized condiments (9). Also, CAP is an intriguing compound, as the ingestion of chilli peppers can elicit both pleasure and adverse experiences, shaped by personal preferences and consumption patterns. Consequently, its effects transcend flavor, enhancing our comprehension of its potential health benefits for humans (8).

The biosynthesis of CAP in Capsicum species is probably preserved owing to its functions in seed germination and pest deterrence (10). This phytochemical is unevenly distributed in the pepper fruit, being concentrated in the placental tissue enclosing the seeds, which directly facilitates its protective role in seed germination (11). The aversion to substantial quantities of CAP prevents rats and other mammals, hence increasing germination probabilities, as these animals can chew and ingest the seeds, preventing their sprouting (12). Conversely, birds exhibit insensitivity to the acrid flavor, and their gastrointestinal systems enable the survival of pepper seeds, rendering them great dispersers (13). Moreover, CAP preserves plants against pests such as flies and mold, and people have utilized this characteristic for infection treatment and food preservation (14,15). Although taking excessive amounts of chilli peppers may cause discomfort, the phytochemical under review can offer analgesic benefits when utilized correctly. The dual nature has drawn interest from scholars for years, enhancing our comprehension of CAP (16).

CAP was initially isolated in 1876, and its structure was elucidated in 1919 (17,18). The structure and characteristics of this phytochemical are currently well defined. Being a nonpolar phenolic chemical, it is insoluble in water and is generally extracted with nonpolar solvents such as ether, benzene, dimethyl sulfoxide, or acetone, although ethanol may also be useful due to its amphipathic characteristics (19). The molecular nature of CAP facilitates its efficient absorption through both topical and oral routes, with absorption rates reaching as high as 94% (20). Upon its discovery and characterization, it was determined that CAP is part of a class of chemicals named capsaicinoids (CADs), exhibiting analogous structural and biological properties, as illustrated in **Figure 1** (20).

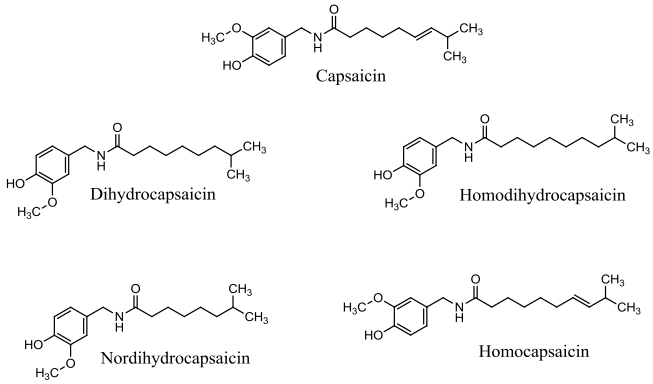

Figure 1. Chemical structures of CAP and some CADs

3.2. CAP-related phytochemicals

Plants belonging to the capsicum genus biosynthesize numerous compounds similar to CAP, which are referred to as CADs. These compounds include dihydrocapsaicin, nordihydrocapsaicin, homodihydrocapsaicin, and homocapsaicin, as illustrated in **Figure 1** (21). Although these compounds exhibit structural similarities to CAP, they are less common. This is because CAP may comprise up to 80% of the CAD content in chilli peppers (22,23). The benzene ring structure primarily determines the pungency of CADs, but changes in the acyl chain length can also influence this property (24). In addition to CADs, there are additional associated chemical groups, including capsinoids, which exhibit diminished pungency, and highly potent resiniferous compounds (25,26). Significantly, research has utilized these CAP-related substances to increase their understanding of disease mechanisms and pain, demonstrating that CAP can paradoxically both

produce pain as well as offer insights into pain alleviation approaches (5,27).

3.3. CAP and its related pain properties

Research on pain-related phenomena has extensively used CAP because it selectively excites nociceptive neurons (28). In this topic, the authors have discussed some of the pathways through which CAP causes pain, highlighting its crucial role in our current understanding of the neural systems underlying pain.

3.3.1. The significance of CAP in a pain investigation

Intradermal CAP injections were utilized to cause primary and secondary hypersensitivity in rats and monkeys to both dangerous and harmless stimuli prior to the discovery of the CAP-activated receptor (29,30). Early research revealed that CAP increases ion influx, specifically calcium, in dorsal root ganglion (DRG) neurons, hence activating nociceptors (31,32). Eventually, the process by which CAP produces pain was elucidated by the cloning of the transient receptor potential cation channel subfamily V member 1 (TRPV1) receptor (33). This discovery, which revealed that CAP causes pain-like behaviors by activating TRPV1 receptors on nociceptors—previously known as vanilloid receptor 1 (VR1)—was important for our knowledge of pain mechanisms (33). By demonstrating that a receptor-coupled channel in nociceptors monitors environmental stimuli, which causes depolarisation and, ultimately, pain, this finding revolutionized our knowledge of pain mechanisms. Since pain can result from genetic abnormalities affecting these proteins, it also opened up new options for medication development (34).

Later in vivo research revealed that TRPV1 receptor-deficient mice exhibited lowered heat-stimulus responses and decreased paw-licking produced by CAP (35). Whole patch-clamp methods demonstrated that these mice had reduced DRG neuronal calcium influx (35). Therefore, the use of CAP in animal models proved essential in clarifying TRPV1's function and improving our comprehension of how pain is processed and modulated. All things considered, the identification of TRPV1 was essential for the validation of CAP-induced pain models. These models are currently used to study the neural underpinnings of pain and to test novel TRPV1 antagonists and medications that aim to block the effects of TRPV1 activation before going through clinical trials.

3.3.2. Mechanisms of CAP-inducing pain

The CAP-evoked response of C-fibers in the cat saphenous nerve was one of the first examples of CAP selective action on C-polymodal nociceptors. Furthermore, injections of CAP decrease the thermal thresholds in humans and rats (36), demonstrating the selective action of CAP on these nociceptors as well as the thermodependency of sensory responses in both animals (36). G-proteins and protein kinases (PKA and PKC) are involved in the mechanisms behind CAP-induced mechanical allodynia in the spinal cord; these effects can be counteracted by inhibiting PKC and PKA. For example, kinase activity can boost surface expression and trafficking of different molecules while also improving receptor functioning (37). By phosphorylating the NMDA receptor subunit NR1 at particular serine residues, CAP stimulates PKA and PKC, increasing receptor activity.

Moreover, CAP phosphorylates p38 MAPK, a member of the mitogen-activated protein kinase (MAPK) family, in the dorsal horn tissues of the spinal cord and peripheral tissues (38), suggesting a function for MAPK in pain-related disorders. CAP-induced central sensitization's intracellular mechanisms have been clarified by inhibiting these kinases. The neuropeptide CGRP is another essential component in central sensitization. CAP activates TRPV1, which in turn causes the spinal cord to generate CGRP. Mechanical hyperalgesia and secondary allodynia can be lessened by inhibiting CGRP receptors (39).

Another useful tool for demonstrating the function of reactive oxygen species (ROS) in central sensitization is the CAP-induced pain model. In addition to their pro-hyperalgesic actions, ROS alters redox-sensitive protein residues and hence impacts pain pathways (40). Tempol (4-hydroxy-2,2,6,6-tetramethylpiperidine-1-oxyl) and PBN (N-tert-butylnitrone), two ROS scavengers, have been found to reduce dorsal horn neuronal activity, which in turn reduces primary and secondary hyperalgesia (41). This finding raises the possibility that ROS plays a role in the persistence of pain. In addition to nociceptors, keratinocytes are involved in pain signaling. Using the Cre-lox method to produce TRPV1 in keratinocytes, it was discovered that CAP activates these cells, increasing the expression of c-fos in the spinal cord—a behavior linked to nociceptive responses such as paw licking. This demonstrates how nociceptors and keratinocytes interact during pain situations (42).

Our knowledge of the mechanisms underlying stomach pain, especially in instances of irritable bowel syndrome, has improved because of CAP. Injections of intrathecal CAP can cause mechanical hyperalgesia and behaviors connected to pain, which suggests a nociceptive response as opposed to normal grooming behavior (43). Similar hyperalgesia and allodynia are reported in patients with this syndrome (44), indicating that TRPV1 agonists can activate nociceptive fibers in the colon and identify these receptors as possible therapeutic targets. In models of dextran sulfate sodium-induced colitis, TRPV1 also co-localizes with substance P and CGRP, highlighting their functions in visceral pain signaling (45).

Studies using functional magnetic resonance imaging demonstrate that injections of CAP in wild-type rats activate certain pain brain circuits, providing additional evidence for the importance of TRPV1 receptors. Reduced activation in these brain locations is the result of TRPV1 receptor loss, suggesting a supraspinal regulation of TRPV1

in pain perception (46). TRPV1 also affects the psychological components of visceral (35). TRPV1/CGRP pathway regulation is important in arthritis (48). While CGRP antagonists can reduce neuronal firing generated by CGRP and MIA, intra-articular CGRP injections have been demonstrated to lower mechanical thresholds and increase sensitized fiber activity in both normal and mono-iodoacetate-induced arthritic animals (49). This implies that nociceptor sensitization and joint inflammation are strongly influenced by peripheral CGRP release.

Identification of pain-related ligand-receptor and receptor-receptor interactions has advanced significantly in recent years (50). The interaction between CAP and TRPV1 is one of the most notable. When CAP and QX-314 are administered together, the membrane-impermeable sodium channel blocker becomes more accessible. This prevents sodium from entering CAP-sensitive DRG neurons (51), hence causing analgesia. Nevertheless, neither the impact of TRPV1's pore size nor its dynamic permeability to ions of different sizes or charges were examined in this investigation. The TRPV1 receptor is known to be a nonselective cation channel since it has a stronger affinity for calcium than for sodium. In just a few seconds, CAP and other TRPV1 agonists can change the pore size of TRPV1, producing effects that could continue for many minutes (52). This allows for time-dependent discrimination between monovalent and divalent cations.

Specifically, PKC phosphorylates TRPV1's serine 800 residue, which increases permeability to larger cations, sensitizing TRPV1 and boosting inward currents to allow neurons to discriminate between cation sizes (52). PKC specifically phosphorylates serine 800 in rat DRG neurons but not serine 502, which increases pain in an osteoarthritis model produced by MIA. In this model, CAP-induced pain behaviors can be mitigated by blocking PKC but not PKA (53). Ion selectivity and discrimination patterns vary amongst TRPV1 agonists, including piperine, NADA, and resiniferatoxin (RTX). This implies that different TRPV1 agonists may alter the preference for inward ions and that the inward ion fluxes may be influenced by distinct kinases, such as PKA and PKC (54). New research has clarified this subject even more by showing that CAP attaches to a particular pocket on the TRPV1 receptor, emphasizing its special connection (55).

As shown in **Figure 2**, Tmem100's involvement in the mechanism of CAP-induced pain and the phosphorylation at Ser800 permits TRPV1 to discriminate cation inflow (55). The TRPV1-TRPA1 complex is activated in the presence of Tmem100 (A), which raises the inflow of calcium and heightens pain perception. However, since TRPA1 is present in an inactive conformation, the TRPV1-TRPA1 complex causes a reduced calcium influx in the absence of Tmem100 (B) (56). The black arrows indicate the different levels of calcium influx; DRG stands for dorsal root ganglion, ER for endoplasmic reticulum, and PKC for protein kinase C.

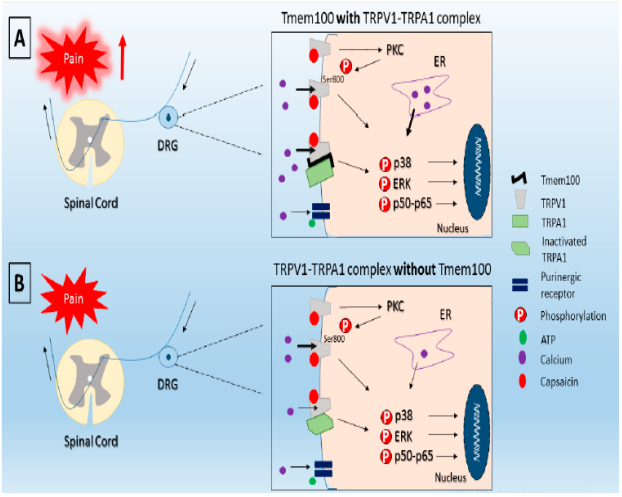

Figure 2. Pain-inducing mechanisms of CAP (56)

CAP exhibits a high affinity, sensitivity, and selectivity for TRPV1, while not activating the analogous TRPV2–TRPV6 receptors. Furthermore, a sophisticated study illustrated the binding of CAP to TRPV1 and identified the specific amino acid residues implicated in this interaction. CAP attaches to TRPV1 in a tail-up, head-down configuration (as described by the authors). The aliphatic tail engages with the channel via nonspecific van der Waals interactions, enhancing binding affinity. Hydrogen interactions between the vanillyl head and amide neck with glutamic acid residues E571 and T551 of the channel confer selectivity for ligand binding (57), as shown in **Figure 3**. Interactions with TRPV1, including Tyr511, Glu570, and Ile569, facilitate the accommodation of CAP within the vanilloid pocket, characterized by the vanillyl head. Conversely, the RTX molecule, a TRPV1 agonist, is larger than CAP and has a distinct electron cloud, preventing its accommodation in the vanilloid pocket, which is too shallow for RTX (58).

The spatial distribution of both compounds elucidates the unique agonist profile and activity, clarifying the superior potency of RTX in comparison to CAP (59). Alongside spatial allocation, the structure-activity connection analysis elucidates the functional categories that are crucial to these differences. The amide group is crucial for CAP action, whereas the five-membered diterpene ring serves this function for RTX (60). These investigations significantly influenced the understanding of the essential sites for CAP or other agonist binding and the activation of TRPV1 (61). Consequently, these investigations facilitate future pharmaceutical strategies grounded in this understanding, as these agonists may function as both pro-hyperalgesic and anti-hyperalgesic, which will be further upon in the subsequent section.

As shown in the **Figure 3**, regarding a tail-up, head-down configuration, CAP binds to TRPV1 to enhance the influx of calcium (56). The activation of calcium-dependent enzymes such calcineurin, which dephosphorylates TRPV1 (62),

downregulates HVACC (63), and ultimately results in TRPV1 desensitization, is a secondary impact of calcium influx. Additionally, by vying for the same intracellular compartment, calmodulin stops ATP-induced sensitization of TRPV1 (64).

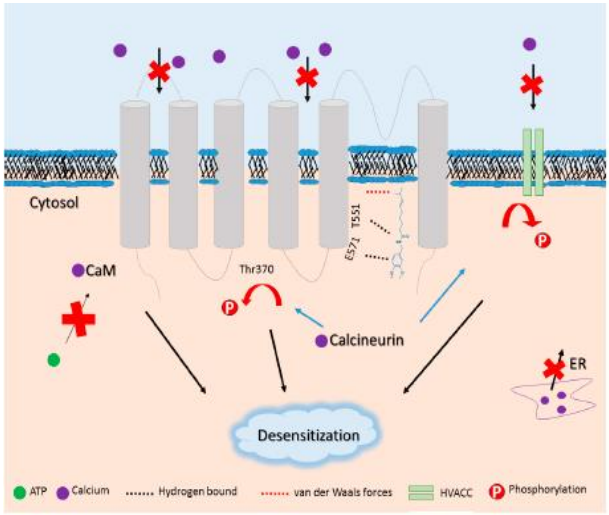

Figure 3. Desensitization and interaction mechanisms between CAP and TRPMV1 (56)

TRPV1-TRPA1 is a well-researched receptor-receptor interaction (65). This connection is ascribed to the creation of a heterodimer between TRPV1-TRPA1 receptors (66), which is made feasible by the establishment of a receptor cluster in neurons (67) and the migration of lipid rafts. Recent research has shown that the trans-membrane receptor Tmem100, which functions as an adapter molecule to regulate the activity of DRG neurons, is co-expressed with the TRPV1-TRPA1 complex. However, it is also feasible for the TRPV1-TRPA1 complex to assemble without Tmem100. Since TRPA1-positive DRG neurons show a decrease in inward current in response to a stimulus such as mustard oil (a TRPA1 agonist), but not CAP, TRPV1 suppresses TRPA1 activity in the TRPV1-TRPA1 complex in the absence of Tmem100. However, TRPV1 increases TRPA1 activity and potentiates pain perception when Tmem100 is present (56). Furthermore, PKA activation is encouraged by TRPA1-initiated calcium influx, which sensitizes TRPV1 channels (68). Consequently, a complicated interaction between CAP and other agonists and TRPV1 illuminates the intricate mechanism involved in TRPV1 regulation. Complexity is increased by TRPV1 crosstalks with other receptors, which develop a completely distinct pharmacology (69).

3.3.3. TRPV1 as a target for natural products

Presently, CAP-induced discomfort is utilized to evaluate novel compounds that interact with the TRPV1 receptor. A substantial amount of research indicates that products obtained from natural products may serve as potential pharmaceuticals (70). It is recently demonstrated that the flavonoids naringenin (71), vitexin (72), and hesperidin methyl chalcone mitigate inflammatory pain by partially targeting CAP-activated TRPV1 receptors (73). Other flavonoids, like eriodictyol and hesperidin, similarly target TRPV1 to alleviate pain (74), while silymarin mitigates gastritis (75). These observations support the notion that flavonoids regulate TRPV1. Furthermore, additional compounds like β-spinasterol extracted from the leaves of the medicinal plant Vernonia tweedieana exhibit antinociceptive effects through TRPV1 antagonism (76).

Curcumin, a prominent natural product-derived chemical, possesses over 100 distinct targets, including TRPV1 (77). Curcumin mitigates the increase in calcium levels and inward current generated by CAP in dorsal root ganglion neurons of both mice and rats by antagonizing TRPV1 receptors (78). In light of the widespread occurrence of chronic pain and the significance of TRPV1, the pharmaceutical sector has concentrated its endeavors on the creation of synthetic medications aimed at TRPV1 (79). These pharmaceuticals are categorized as TRPV1 antagonists and TRPV1 agonists (80), with both classifications exhibiting significant drawbacks.

TRPV1 agonists may induce discomfort and/or erythema prior to the onset of desensitization, while TRPV1 antagonists generally exhibit reduced efficacy relative to TRPV1 agonists and may lead to hyperthermia (81). SB-705498 was among the initial TRPV1 antagonists produced. A single oral dose of 400 mg of SB-705498 diminishes CAP-induced flare and increases the heat threshold in patients (56). Hyperthermia is a significant adverse effect associated with the treatment of TRPV1 antagonists. The administration of lesser dosages (2 and 8 mg) of AMG 517 induces hyperthermia, with temperatures ranging from 39 to 40.2 °C. Conversely, the repeated administration of this medicine for 7 days at a dosage of 10 mg diminishes hyperthermia, indicating a dose-dependent impact and desensitization (82).

3.3.4. Mechanisms of CAP-inducing analgesia

Not only does CAP cause pain, but it also has other impacts on nociception. In actuality, analgesia follows an initial pain sensation that is induced by large or repeated doses of CAP (83). It was shown that this reduction of sensitivity to unpleasant stimuli occurred in response to mechanical, chemical, and thermal noxious stimuli (84).

More research is being done on the underlying pathways of CAP-induced analgesia. The TRPV1 receptors enter a refractory condition known as desensitization upon exposure to a large or repetitive dosage of CAP, which results in the suppression of receptor activity (85), as shown in **Figure 3**. Desensitization to CAP is caused by mechanisms that are not fully understood. However, evidence suggests that this mechanism involves the depletion of neuropeptides, such as substance P, in the TRPV1-expressing nerve fibers (86), as well as the blocking of high-voltage-activated (HVA) calcium channels, which

raises intracellular calcium levels (87). The activation of calcium-dependent proteins, which results in the desensitization of TRPV1, is a delayed or secondary impact of calcium influx (88).

TRPV1's cytosolic ankyrin repeat domain (ARD) has a multi-ligand binding that enables intracellular ATP binding to certain pockets of TRPV1-ARD and sensitizes this receptor. However, the mutation in these pockets reduces desensitization in the absence of ATP, meaning that desensitization of TRPV1 happens when calmodulin binds in the same pockets of ATP in a calcium-dependent manner (89). Particularly, Thr370 residues that were previously phosphorylated by PKA are dephosphorylated by the calmodulin and calcium-dependent enzyme calcineurin. Furthermore, this enzyme inhibits HVA calcium channels, which limits the amount of calcium that enters DRG neurons, as previously shown in **Figure 3**. Taken together, these pathways cause TRPV1 to become desensitized and explain how CAP produces analgesia (5).

Apart from the desensitization mechanism of TRPV1, recent data has demonstrated the effectiveness of CAP as an analgesic (90). TRPV1, which is activated by CAP, blocks the Piezo proteins, a class of cation-selective ion channels in mammals that react to mechanical strain (90). Phospholipase C (PLC) is activated in response to calcium and depletes phosphoinositides, which inhibits Piezo proteins. In fact, the inactivation of Piezo channels is reversed and rundown inward current is reduced by injecting phosphoinositides into the cytosol via an excised inside-out patch clamp (90). As a result, the reduction of these phosphoinositides is correlated with the suppression of inward current, which in turn inhibits the mechanical stimulation of piezo channels (90).

The degeneration of sensory fibers is also linked to CAP-induced analgesia (91). The exact pathway by which CAP induces cellular death remain unclear. Apoptosis by caspase activation is one of the most likely mechanisms, according to recent research (92). According to an in vitro study, CAP causes DNA fragmentation and nucleus decrease in a caspase-dependent way as a result of sensory neurons' cell death. Furthermore, there is a direct correlation between the mitochondrial permeability transition and the process of cell death that CAP initiates through TRPV1 (93). Conversely, CAP can induce cell death through bleb formation in the membrane and cell swelling—apoptosis-independent processes. The intracellular concentration of calcium regulates the extracellular sodium influx via TRPV1, which is necessary for these mechanisms to function (94).

In inflammatory situations, CAP-induced analgesia lasts longer than in baseline conditions (95). While a 10-gram intraplantar injection of CAP in control mice resulted in analgesia for two days, the same dose of CAP generated analgesic effects for six and thirty days, respectively, in animals primed with carrageenan or CFA (96). The increase in CAP-induced analgesia during inflammation is probably caused by TRPV1 expression (97), which facilitates TRPV1 desensitization. Supraspinal processes influence CAP-induced analgesia in addition to peripheral alterations. In a rat under anesthesia, the subcutaneous injection of CAP dramatically lowers the jaw-opening reflex and raises the withdrawal threshold to mechanical stimulation; both effects are countered by microinjecting an opioid or dopaminergic antagonist into the nucleus accumbens. CAP-induced analgesia modulation also involves the tonic GABAergic suppression of neurotransmission in the rostral ventromedial medulla (RVM) (98).

It is agreed that CAP-induced suppression of the jaw-opening reflex can be avoided by injecting muscimol (a GABA-A receptor agonist) but not naloxone in the RVM (99). Intrathecal injection of GABA-B and opioid receptor antagonists neutralized this analgesic effect, suggesting that activation of inhibitory spinal receptors is a key mechanism of CAP-induced analgesia (100). Twenty minutes after a subcutaneous injection of CAP, proopiomelanocortin mRNA expression—a precursor to endorphin—shows an increase in opioid activity in the arcuate nucleus of the rats' hypothalamus, as shown in **Figure 4** (101).

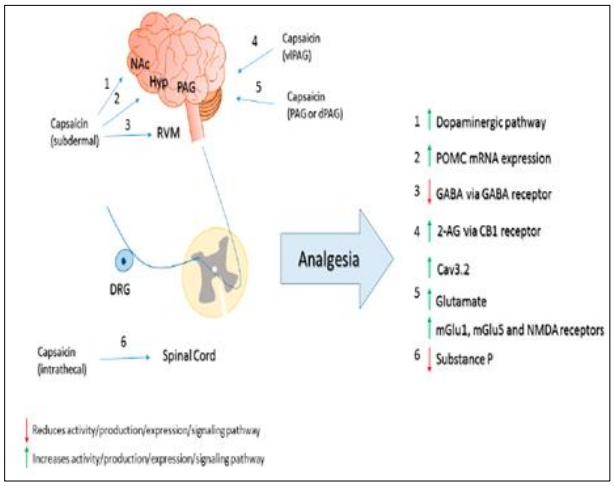

Figure 4. Supraspinal mechanisms of CAP-induced analgesia (56)

Given **Figure 4**, subdermal injection of CAP produces analgesia by modulating the dopaminergic pathway in the N-acetylcysteine (entry 1) (56), opioid pathway in the hippocampus (entry 2), and GABAergic activity in the RVM (entry 3). In addition, ventrolateral periaqueductal gray matter injection of CAP activates the endocannabinoid pathway (entry 4) (102), and dorsal periaqueductal gray by modulating the glutamate signaling pathway (entry 5) (103). Intrathecal injection of CAP depletes substance P and also produces analgesia (entry 6) (104).

In various focal points, central administration of CAP also results in analgesia. For example, long-term regional analgesia with substance P depletion is produced by

intrathecal injections of CAP or RTX (104). Since mice lacking this receptor exhibit a stronger nociceptive response than wild type mice, the analgesic effect via supraspinal TRPV1 following intracerebroventricular injection of CAP depends on the activation of Cav3.2 channels (105). A brief period of hyperalgesia may precede the production of anti-nociception to thermal stimulation following the microinjection of CAP into the periaqueductal grey or its dorsal periaqueductal gray in rats (106). The release of glutamate and the local activation of TRPV1, mGlu1, mGlu5, and NMDA receptors are prerequisites for CAP analgesic impact in the PAG. In the RVM, there is also an increase in OFF-cell activation and a decrease in ON-cell activation (106). CAP injections into the ventrolateral periaqueductal gray in an animal model of diabetic neuropathy decrease thermal hyperalgesia (107).

Inhibitory descending pain pathways are activated by the injection of CAP into the ventrolateral periaqueductal gray. The local TRPV1 activation in ventrolateral periaqueductal gray is responsible for the analgesic action of CAP injection. This activation releases glutamate into RVM, activates OFF-cells, and activates the inhibitory descending pain pathway (108). Moreover, the endocannabinoid-2-arachidonolyglycerol (2-AG) is formed in a manner that is dependent on the Gq-protein-coupled PLC-DAGL pathway as a result of the glutamate released acting on mGlu5 post-synaptic receptors. Consequently, 2-AG causes retrograde disinhibition of GABA release by activating pre-synaptic CB1 receptors. Furthermore, ventrolateral periaqueductal gray exhibits co-expression of TRPV1 and -opioid receptors. Rats exhibiting enhanced glutamate release and reduced ON-cell activity in RVM demonstrate thermal analgesia when sub-doses of CAP and opioid receptor agonists are administered concurrently at this location (5). Rats with streptozocin-induced diabetic neuropathy do not exhibit an overt pain-like response during the inflammatory phase of the formalin test when CAP is injected into the RVM. This effect may be attributed to the up-regulation of TRPV1 receptors in the RVM (109).

In light of the above-described data, CAP has been employed as a pharmacological support agent in the treatment of pain. This phytochemical is an effective treatment for a variety of painful disorders. include neuropathic pain and complicated regional pain syndromes (110), postsurgical neuropathic pain (111), post-herpetic neuralgia (112), and excruciating diabetic peripheral neuropathy (113). Another study suggests that using nasal CAP on a regular basis can stop cluster headache episodes (114). Humans' skin nerve fibers degenerate when topical CAP (0.075%) is given four times a day for three weeks. This reduces sensitivity to cold and tactile stimuli but increases sensitivity to heat and mechanical stimuli (115).

Topical use of an 8% CAP patch resulted in a considerable reduction in pain for 12 weeks in patients with post-herpetic neuralgia (116). On the other hand, the 8% CAP patch was used to reduce the area of allodynia in a patient with post-traumatic neuropathic pain by 80%. Up until the eighteenth month following application, this impact was noted. Additionally, CAP candies applied topically provide momentary relief from the discomfort of oral mucositis, a typical side effect experienced by cancer patients receiving chemotherapy or radiation therapy (117).

Applying CAP topically repeatedly can result in severe burning at both low and high dosages. The initial discomfort brought on by using a single, large dose of CAP is avoided by pretreating with a local anesthetic (118). Long-lasting analgesia in the orofacial region is produced by the combination of CAP administered in a sensory nerve and lidocaine-derived QX-314, a local anesthetic. This combination also prevents the jaw opening reflex in rats that is triggered by stimulation of the tooth pulp (119). Rats undergoing plantar incisional surgery show a reduction in mechanical hypersensitivity 72 hours post-incision and a delay in the onset of mechanical hypersensitivity due to the destruction of TRPV1-expressing afferents following the perisciatic application of lidocaine (2%) or QX-314 (0.2%) combined with CAP (0.05%). However, in naïve mice, there was also a delay in the onset of mechanical hypersensitivity and neurotoxicity symptoms (120). In comparison to the separate application of formulations, the topical combination of 0.025% CAP and 3.3% tricyclic antidepressant doxepin can expedite the onset of analgesia in individuals suffering from neuropathic pain (121).

4. Conclusion

In conclusion, CAP is a crucial molecule in pain research and therapeutic applications, possessing the ability to elicit pain while also exhibiting notable analgesic characteristics. Comprehending the pathways by which CAP interacts with the TRPV1 receptor has clarified mechanisms for pain regulation and unveiled opportunities for novel pain management techniques. The dual nature of CAP, functioning as both a nociceptive agent and a possible analgesic, highlights its complexity and significance in clinical contexts. The numerous applications of CAP, especially in topical preparations and in conjunction with other analgesics, underscore its therapeutic potential for addressing many pain problems. Subsequent research should persist in investigating CAP and its equivalents, with the objective of enhancing their application in pain management while tackling the issues of side effects and individual response variability. A comprehensive understanding of CAP's diverse functions may result in more effective and customized pain management strategies.

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هل الكابسيسين مسبب للألم أم قاتل للالم؟ مراجعة للآليات المرتبطة به

الخلاصة:

المقدمة: الكابسيسين هو المادة الكيميائية المسؤولة عن الخصائص الحارة والمزعجة للفلفل الحار. ولأنه ينتج الحرارة والألم، فإن هذه المادة الكيميائية النباتية هي وسيلة قيمة للاستثمار العلمي في أبحاث الألم. **الهدف:** تدرس هذه الدراسة العمليات الكامنة وراء الألم الناجم عن الكابسيسين، مع التأكيد على أهميتها في فهم تعديل آلام الدماغ. كما تسلط الضوء على الاستخدامات العلاجية للكابسيسين في إدارة الألم وخصائصه المسكنة. علاوة على ذلك، فإن الهدف الرئيسي هو فهم الدور المزدوج للكابسيسين بشكل أفضل كمحفز للألم ومسكن للألم. **طرق العمل:** جمع المؤلفون البيانات من العديد من الدراسات المنشورة الملخصة من العديد من منصات الفهرسة، بما في ذلك Scopus وWeb of Science وGoogle Scholar وPubMed، بين عامي 2015 و2024. **النتائج:** توضح النتائج أن الكابسيسين يعمل في البداية كمحفز للألم ولكن مع الاستخدام الموسع، يصبح مسكنًا ممتازًا للألم. **الاستنتاج:** نظراً لدوره النشط في تنظيم الألم، يمكننا اعتبار الكابسيسين نموذجاً مثيراً للاهتمام لفهم الآلية الجزيئية وراء إحداث الألم وتخفيفه.

الكلمات المفتاحية: كابسيسين؛ TRPA1؛ الألم العصبي؛ الطعم اللاذع؛ جنس الفلفل الحار.