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Abstract

Capsaicin (CAP) is the chief active ingredient of natural chili peppers. It has culinary and medicinal benefits. CAP activates its receptor, transient receptor potential vanilloid subfamily 1 (TRPV1), which is expressed in the sensory and motor neurons, adipocytes, liver, vascular smooth muscle cells, neuromuscular junction, skeletal muscle, heart and brain. The specificity of CAP to activate TRPV1 is the fundamental mechanism for its medicinal benefits to treat pain, obesity, hypertension, and other diseases. Preclinical data from rodent model of high fat diet-induced obesity collectively suggest that CAP exerts its effects by activating TRPV1 signaling pathway, which stimulates thermogenic mechanisms in the white and brown adipose tissues to induce browning of white adipose tissues and brown adipose tissue thermogenesis. This leads to enhancement of metabolic activity and thermogenesis to counter obesity. Although CAP and its pungent and non-pungent analogs are used in human clinical studies, their effects on satiety and energy expenditure have been the highlights of such studies. The precise mechanism of action of CAP has not been evaluated in humans. This article summarizes these data and suggests that long-term safety and tolerance studies are important for advancing CAP to treat human obesity.

Keywords: capsaicin, TRPV1, weight gain, obesity, adipose tissue, browning, brite, chili peppers, satiety, energy expenditure

1. Introduction

Capsaicin (CAP) is the most commonly occurring capsaicinoids in chili peppers. It is enriched in the pith and ribs of the pepper. The pungency and heat of CAP give a prominent place...
as a chief spice ingredient in food industry. Chili peppers contain both pungent CAPoids and non-pungent capsinoids (Figure 1). CAP and dihydrocapsaicin belong to the group of pungent capsaicinoids, while non-pungent capsinoids like capsiate, dihydrocapsiate and nordihydrocapsiate have also been shown in preclinical studies to be beneficial against metabolic diseases. Chemically, CAP is known as 8-Methyl-N-vanillyl-trans-6-nonenamide. Biologically, CAP binds to and activates its receptor transient receptor potential vanillloid subfamily 1 (TRPV1) predominately expressed at the sensory nerve endings. Activation of TRPV1 by CAP is responsible for the intense heat and burning. CAP desensitizes TRPV1 and exerts its analgesic activity.

1.1. TRPV1: capsaicin receptor

TRPV1 is the first member of the vanillloid subfamily of the TRP superfamily of proteins. It is a non-selective cation channel protein discovered by Michael Caterina [1]. TRPV1 consists of six transmembrane domains, with intracellular N and C termini. The ion channel pore region is situated between the fifth and sixth transmembrane domains. Although CAP and resiniferatoxin are exogenous activators of TRPV1, it is endogenous activation is regulated by heat (~43°C), acidic pH (~5.5) and by inflammation mediators. Primarily, the expression of TRPV1 is recognized in sensory neurons. Published literature suggests that TRPV1 is also expressed in various other tissues such as the neuromuscular junction [2–4], adipose tissue [5–7], liver [8, 9], skeletal muscle [10, 11], vascular smooth muscle [12], etc. Also, published work suggests that TRPV1 in the brain. TRPV1 is involved in experimental model of temporal lobe epilepsy (TLE) [13]. Although TRPV1 expression has been reported in some brain areas [14], it is still

Figure 1. Structure of capsinoids and capsaicinoids.
<table>
<thead>
<tr>
<th>Treatment</th>
<th>Condition</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Topical cream 0.01 or 0.025% for 6 weeks</td>
<td>Psoriasis vulgaris</td>
<td>Beneficial</td>
</tr>
<tr>
<td>Topical cream 0.075% for 8 weeks</td>
<td>Painful diabetic neuropathy</td>
<td>Beneficial</td>
</tr>
<tr>
<td>Topical cream 0.05% for several days</td>
<td>Idiopathic trigeminal neuralgia</td>
<td>Beneficial</td>
</tr>
<tr>
<td>Topical cream: 0.075% or 0.025% for 2 months</td>
<td>Post mastectomy pain syndrome</td>
<td>Beneficial</td>
</tr>
<tr>
<td>Topical cream 0.025% for 7 days</td>
<td>Cluster headaches</td>
<td>Beneficial</td>
</tr>
<tr>
<td>Topical cream 0.025% for 3 weeks</td>
<td>Solar (brachioradial) pruritus</td>
<td>Beneficial</td>
</tr>
<tr>
<td>Oral candy (taffy): 5–9 ppm</td>
<td>Oral mucositis pain</td>
<td>Beneficial</td>
</tr>
<tr>
<td>Topical cream 0.075% for 4, 8 and 12 weeks</td>
<td>Chronic distal painful polyneuropathy</td>
<td>No beneficial effects</td>
</tr>
<tr>
<td>Intravesical injection 2 mM</td>
<td>Chronic traumatic spinal detrusor hyperreflexia</td>
<td>Beneficial</td>
</tr>
<tr>
<td>Intravesical injection 10 μM for 1 month (twice weekly)</td>
<td>Severe bladder pain</td>
<td>No beneficial effects</td>
</tr>
<tr>
<td>Intranasal solution (0.1 mMol/L) every 2 or 3 days. Seven total treatments</td>
<td>Non-allergic, non-infectious perennial rhinitis</td>
<td>No beneficial effects</td>
</tr>
<tr>
<td>Topical cream: 0.075% for 8 weeks or 0.025% for 4 weeks</td>
<td>Neuropathic pain</td>
<td>Beneficial</td>
</tr>
<tr>
<td>Intravesical solution: 100 ml of 2 mM for 30 min.</td>
<td>Refractory detrusor hyperreflexia</td>
<td>Beneficial</td>
</tr>
<tr>
<td>Topical: 0.025% for 4 weeks</td>
<td>Atypical odontalgia</td>
<td>Beneficial</td>
</tr>
<tr>
<td>Topical cream: 5–10%</td>
<td>Refractory pain</td>
<td>Beneficial</td>
</tr>
<tr>
<td>Topical cream: 0.075% for 4 weeks (four times a day)</td>
<td>HIV-associated distal symmetrical peripheral neuropathy</td>
<td>No beneficial effects</td>
</tr>
<tr>
<td>Intravesical solution (Pelargonic acid vanillamide): 0.5 ml of 0.1 mmol/L solution per administration. Seven times in 14 days</td>
<td>Perennial allergic rhinitis</td>
<td>No beneficial effects</td>
</tr>
<tr>
<td>Topical cream</td>
<td>Painful osteoarthritis</td>
<td>Beneficial</td>
</tr>
<tr>
<td>Topical cream 0.025% for 6 weeks</td>
<td>Prurigo nodularis</td>
<td>Beneficial</td>
</tr>
<tr>
<td>Oral red pepper powder 5 g/day for 5 weeks</td>
<td>Functional dyspepsia</td>
<td>Beneficial</td>
</tr>
<tr>
<td>Topical liniment 0.05% for 5 days (three times a day)</td>
<td>Hemodialysis-related pruritus</td>
<td>Beneficial</td>
</tr>
<tr>
<td>Topical ointment 0.006% for 4 weeks</td>
<td>Intractable pruritus ani</td>
<td>Beneficial</td>
</tr>
<tr>
<td>Oral capsaicin 0.25%</td>
<td>Burning mouth syndrome</td>
<td>Beneficial</td>
</tr>
</tbody>
</table>
Table 1. Capsaicin (type and dose) target disease effect.

<table>
<thead>
<tr>
<th>Capsaicin Formulation</th>
<th>Disease Target</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transdermal oleic capsaicin: containing patches 3 g per patch on 2 days with a 2-day interval between trials</td>
<td>Stable coronary disease (to improve ischemic threshold)</td>
<td>Beneficial</td>
</tr>
<tr>
<td>Oral troche: 1.5 μg per troche. One troche per meal for 4 weeks</td>
<td>Swallowing dysfunction</td>
<td>Beneficial</td>
</tr>
<tr>
<td>Topical cream 0.075%</td>
<td>UV induced immunosuppression</td>
<td>Beneficial</td>
</tr>
<tr>
<td>Transdermal dermal patch: 640 μg/cm², 8% w/w for 60 min</td>
<td>HIV-associated peripheral neuropathy</td>
<td>Beneficial</td>
</tr>
<tr>
<td>Intraoperative wound instillation of ultra purified CAP instillation</td>
<td>Post herniotomy pain</td>
<td>Beneficial</td>
</tr>
<tr>
<td>Topical ointment: 0.03% for 4 weeks (four times a day)</td>
<td>Uremic pruritus</td>
<td>Beneficial</td>
</tr>
<tr>
<td>CAP dermal patch: 8 or 0.04% for 30, 60 and 90 min</td>
<td>Post herpetic neuralgia</td>
<td>Beneficial</td>
</tr>
<tr>
<td>Topical capsaicin cream 0.05% for 3 weeks (thrice a day)</td>
<td>Chronic soft tissue pain</td>
<td>Beneficial</td>
</tr>
<tr>
<td>Topical civamide cream: 0.075% for 12 weeks (thrice a day)</td>
<td>Osteoarthritis of the knee</td>
<td>Beneficial</td>
</tr>
<tr>
<td>CAP hydrogel patch: 0.1% for 4 weeks (12 h a day)</td>
<td>Myofascial neck pain</td>
<td>No beneficial effect</td>
</tr>
<tr>
<td>CAP cutaneous patch: 8% for 30 to 60 min</td>
<td>Peripheral neuropathic pain</td>
<td>Beneficial</td>
</tr>
<tr>
<td>CAP Cutaneous patch 8% for 60 min</td>
<td>Persistent inguinal postherniorrhaphy pain</td>
<td>No beneficial effects</td>
</tr>
<tr>
<td>Topical CAPoid cream 0.01% nonivamide for 30 min a day for 21 days</td>
<td>Chronic low back pain</td>
<td>Beneficial</td>
</tr>
<tr>
<td>Oral capsules 0.4 mg per capsule (once daily for 2 weeks followed by twice daily for 2 weeks)</td>
<td>Chronic cough</td>
<td>Beneficial</td>
</tr>
<tr>
<td>Oral Yanjiao 425 chili peppers containing 4 mg/g of CAP</td>
<td>Gestational diabetes mellitus</td>
<td>Beneficial</td>
</tr>
<tr>
<td>1.25 g per day for 4 weeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Topical liposomal CAP 0.025% for two 6-week blocks with a gap of 2 weeks</td>
<td>Post-herpetic neuralgia</td>
<td>No beneficial effect</td>
</tr>
<tr>
<td>CAP cutaneous patch</td>
<td>Lumbosacral pain</td>
<td>Beneficial</td>
</tr>
<tr>
<td>CAP cutaneous patch 8% for 60 min</td>
<td>Neuropathy and painful diabetic peripheral neuropathy</td>
<td>Beneficial</td>
</tr>
<tr>
<td>Topical CAP gel: 0.01% or 0.025% for 14 days (thrice a day)</td>
<td>Burning mouth syndrome</td>
<td>Beneficial</td>
</tr>
</tbody>
</table>
highly controversial. Nonetheless, the activation of TRPV1 and its ability to sense pain signaling mechanism make it a valuable target for treating pain in humans.

Recent research has dramatically advanced TRPV1 as a target for treating various human diseases. Table 1 describes a list of preclinical and clinical studies for the beneficial effects of CAP against diseases.

Also, several preclinical and clinical studies have indicated that either capsiate alone or in combination with CAP is beneficial to counteract obesity and increase energy utilization [60–64]. However, the mechanisms behind such effect of CAP or capsiate still remain elusive.

2. Obesity and metabolic dysfunction

Obesity is a major health care issue in the world. About one third of the world's population is either obese or overweight. When energy intake exceeds energy expenditure, the excess energy is stored as triglycerides in the white adipose tissues. This leads to increase in adiposity, which presents glucose intolerance, insulin resistance, dyslipidemia and metabolic dysfunctions. Thus, diet-induced obesity progressively leads to type 2 diabetes, hypertension, hypercholesterolemia, and cardiovascular diseases. Although diet restriction and exercise are good strategies to combat obesity, lack of consistent motivation to stick to healthy diet and regular exercise regimen leads to rebound weight gain when such interventions are stopped. Further, the pharmacotherapy for weight loss is associated with toxicities and side effects [65–68]. Bariatric surgeries are invasive procedures, not easily reversible but associated with high cost and potentials for adverse events.

2.1. CAP for obesity

There are overwhelming evidences for the effectiveness of CAP, its analogs and the whole chili pepper to ameliorate diet-induced obesity in rodents and humans [5, 69–72]. Majority of these research studies have been directed to analyze broader outcome in terms of increase in energy expenditure, metabolic activity or measurement of weight loss. Scientific research unambiguously supports the concept that activation of CAP receptor is important for the effect of CAP to counter diet-induce obesity [5–7, 73]. However, it still remains unclear whether TRPV1 expressed on adipose tissues or on the nerves that innervate the adipose tissues. Further, there is no direct evidence to either support or disregard the role of TRPV1 expressed in central nervous system in this process. Although further research is warranted to clarify these mechanisms, published research works unambiguously support the benefits of CAP in abating obesity and metabolic syndrome in rodent models and humans. This article will discuss mechanisms emerging from studies focused on rodent models of obesity, which have translational value and help to interpret such mechanisms relevance to humans.

2.2. CAP and satiety

Since CAP is a pungent principle in chili peppers, its pungency has been regarded to satiety. Published work suggests that decreased appetite and increased energy expenditure were observed in humans who received red pepper in diet [74]. However, the ability of nonivamide,
a less pungent analog of CAP to reduce appetite [75] suggests that the pungency of CAP may not be directly related to the appetite regulation. Table 2 below summarizes the clinical data that on the appetite regulation of CAP in the form of chili pepper powder or analog.

One important point to remember is the form of CAP that is used for human studies that have yielded contradictory data on the effect of CAP on energy intake. The discrepancy in the quality and type of CAP and variability in the duration of exposure of CAP to participants make interpretation difficult. These studies also lack validations on the ability of the form or type of CAP to activate TRPV1. This must be addressed in future studies. Nonetheless, important questions regarding how CAP mediates satiety or enhances energy expenditure in humans still remain unclear. Research studies focusing the effect of CAP on animal models of obesity will be invaluable to analyze such mechanism(s).

2.3. Adipose depots, functions and TRPV1 expression

Obesity is characterized by increased adiposity. White adipose tissue (WAT) primarily performs the function of insulation and protection in the body, and is regarded as the store for fat as triglycerides. Brown adipose tissue (BAT) plays a critical role in expending energy as it burns the stored energy into heat by a process called thermogenesis. These adipocytes were classified based on their functions and they significantly differ in their mitochondrial content, expression of genes/proteins that regulate thermogenic mechanisms and their localization in the body. BAT represents a small portion depot located throughout the human body at numerous distinct places, especially within the chest (perivascular-around the aorta, common carotid artery, cardiac veins and brachiocephalic artery), visceral cavity and subcutaneous region. BAT occurs along hollowed tissues (heart, trachea, lungs and esophagus), and in the visceral region, it is present around colon pancreas, kidneys, adrenal, liver and spleen [83–87]. Recently, a third type of adipose tissue called beige tissue or brite (brown in white) has been recognized, which are derived from WAT but express BAT specific thermogenic genes and proteins. In mammals, the beige-able adipose tissue locations haven identified as subcutaneous, inguinal and visceral [88] in rodents and supraclavicular [88], perirenal, visceral and subcutaneous depots [89] in humans. Recent research has also characterized the expression of TRPV1 in these tissues. TRPV1 expression has been shown on cultured adipocytes [90–92] and epididymal, subcutaneous and brown adipocytes [6, 7, 93]. The validation of expression of TRPV1 on adipose tissues suggests a plausible role of TRPV1 in the recruitment of BAT activity and thermogenesis and the induction of the molecular conversion of WAT to beige like cells.

2.4. CAP and browning of white adipose tissue

Beige adipose tissue is characterized by the enhanced expression of thermogenic genes and proteins that are not usually expressed at a higher level in WAT. They show enhanced expression of mitochondrial uncoupling protein-1 (UCP-1), bone morphogenetic protein 8b (BMP8b), and central metabolic sensor, sirtuin-1 (SIRT-1), peroxisome proliferator activated receptor gamma (PPARγ) and PR domain 16 containing protein (PRDM-16) and PPARγ coactivator 1α (PGC-1α), which are recognized as factors regulating the beiging of WAT [94, 95]. Further, published literature suggests that Cd137 [96], Shox2 [97], Cited 1 [88], Tmem26 [96], Tbx1 [96, 98], Bmp8b [99–101], ucp-1 [102, 103], SIRT-1-dependent mechanisms [6, 104], are considered
as markers for browning of WAT. Research work suggests that posttranslational modification, such as deacetylation, of PPARγ and PRDM-16 by SIRT-1 is involved in the beiging of WAT [6]. The deacetylation and stabilization of PPARγ and PRDM-16 by SiRT-1 been shown to induce browning of WAT in rodents [6, 7, 104]. CAP has been shown to induce browning of WAT in vitro [105] and in vivo [6] by activating SiRT-1 [6].

SiRT-1 plays a pivotal role in the regulation of cellular energy homeostasis. The phosphorylation and activation of SiRT-1 by cellular protein kinases like Ca²⁺/calmodulin-dependent protein kinase kinase β (CaMKKβ [106]), CaMKIIα [6] and 5′-adenosine monophosphate-activated protein kinase (AMPK [6, 107–109]) has been shown to be important for the effect of CAP in browning of WAT. Preclinical data in mouse model of obesity suggests that feeding a high fat diet inhibits the expression and activity of TRPV1 in WAT and dietary CAP reversed it. CAP stimulates a robust Ca²⁺ influx via TRPV1, which stimulates CaMKII/AMPK-mediated SiRT-1 phosphorylation. This subsequently deacetylates PPARγ and PRDM-16 and promotes their stabilization. Figure 2 describes SiRT-1-dependent mechanisms by which CAP enhances the deacetylation of PPARalha and PGC-1alpha to enhance fatty acid oxidation and mitochondrial biogenesis to promote the browning of WAT and counter obesity. However, such a mechanism has not been shown in humans and future studies are needed to address this.

### 2.5. CAP and BAT thermogenesis

Recognition of expression of TRPV1 in BAT poses important questions on the ability of CAP to enhance thermogenesis. Research approaches have aimed at activation of SiRT-1 [110–112], β3 adrenergic receptors [113–115], thyroid hormone, irisin [116, 117] and FGF21 [118] induction in BAT. Studies also suggest that secretory signaling mechanisms from muscle and liver, such as irisin and Fgf21 are also recognized humans [119]. In rodent model, TRPV1 activation protects against high fat diet-induced obesity by stimulating the expression of thermogenic genes and proteins in BAT [7, 105, 120–122]. Further, CAP enhances SiRT-1-dependent deacetylation and interaction of PPARγ and PRDM-16 in BAT [7].

The crosstalk between TRPV1 and beta-adrenergic action (possible mechanism illustrated in Figure 3) has been reported in the literature [123], which could influence an additive effect on the thermogenic mechanisms in BAT. Also, there are data suggesting that TRPV1 expressed on vagal afferents or intestinal mucosal afferents are important for the anti-obesity effect of CAP [124, 125]. Further studies are required to address these mechanisms.
Research studies are now beginning to address the physiological functions of TRPV1 in adipose tissues. TRPV1 activation has been suggested to regulate adipogenesis and thermogenic pathways. It is also possible that along with the expression of TRPV1 on adipose tissue membranes, the expression of TRPV1 on the nerves that innervate adipose tissues may contribute for the browning of WAT and BAT thermogenic mechanisms. This necessitates the development of mouse strains that lack TRPV1 in specific tissues. Such a tool will be invaluable to delineate the precise role of TRPV1 signaling in metabolic tissues.

2.6. Safety and toxicological analyses of CAP

Studies have also addressed to evaluate the short-term and long-term effects of CAP in rodents and humans. In mice, oral administration of semisynthetic powdered CAP at a dose of 0.3125% caused benign tumors in cecum [126]. Chili pepper extract-fed orally at a dose of 800 mg/kg per day in male and 200 mg/kg/day in female showed no toxicity in mice [127]. Mice received CAP at a dose of 1.46 or 1.94 mg/kg by intraperitoneal injection showed increase in gastric cancer [128], while oral gavage of 2 and 10 mg/kg of CAP showed chemoprevention against tumorigenesis [129]. Studies have also demonstrated the oral LD50 of CAP for mouse and rat were 161.2 and 118.8 mg/kg, respectively, [130]. Studies in humans suggest that feeding CAP in Women with gestational diabetes mellitus improved postprandial hyperglycemia,

![Figure 2. Mechanism by which CAP induces browning of WAT. CAP (CAP)-stimulated Ca\(^{2+}\) influx via TRPV1. Activates CaMKII/AMPK-dependent SIRT-1 activation. SIRT-1 deacetylates PPARalpha and PGC-1alpha. This increases fatty acid oxidation and mitochondrial biogenesis to promote browning of WAT, and counters diet-induced obesity.](image-url)
hyperinsulinemia, and fasting lipid disorders [54]. Also, CAP inhalation for cough challenge test had no single serious adverse event associated with CAP [131]. Further, a study in humans suggests that oral administration of 2.56 mg of CAP with every meal increased satiety and fullness and prevented over eating [77]. However, recent studies show that when along with a high fat diet CAP did not alter energy intake in mouse [6, 7]. However, there is still lack of clear evidence for the long-term effectiveness and safety of CAP in humans. Further studies are required to address this.

3. Conclusions and future perspectives

This article summarizes the preclinical and clinical data, which collectively suggest the anti-obesity effect of CAP. However, the long-term efficacy and safety of TRPV1 agonist remain to be established. Although CAP is a natural product, its pungency is considered as a limitation for oral use. Therefore, research should be geared to develop approaches to mask the pungency of CAP by coating it with polymers of agents, which decrease its burst release in the oral cavity and in the gastrointestinal tract. Since non-pungent analogs have been shown to be effective, efforts should be made to enhance their bioavailability and stability in the body. For example, capsiate, a non-pungent analog of CAP, is effective [62, 64, 132, 133] but issues exist on its stability [134], which requires attention. Recently, a site-specific delivery
system for CAP magnetic nanoparticles for obesity management has been reported [135, 136]. Such approaches should help in advancing the therapeutic efficacy of CAP. Further, efforts to deliver CAP at specific sites in the gastrointestinal tract through formulations such as enteric coated tablets and capsules will be beneficial to prevent its burst release in the stomach. Since human clinical study meta-analyses suggest that both CAPoids and capsinoids are beneficial in enhancing energy expenditure [64], dose products to combine them to counter obesity could be more effective.

Preclinical toxicological studies should be performed to demonstrate the safety and tolerance of CAP. These studies are important to clarify the perceptions that CAP could cause gastrointestinal disturbances and gastric ulcers [137–142]. However, such studies should use quality controlled pure CAP instead of chili pepper powder since the quality of CAP in those powders depends on the source of the peppers. Further, establishing the proof of concept for the anti-obesity effect of CAP using a proper dose and delivery system and validation of its bioavailability and pharmacokinetics are important for advancing its use in humans to treat obesity and associated metabolic complications.

**Conflict of interest**

The authors declare that there are no conflicts of interest.

**Abbreviations**

- **CAP**: Capsaicin
- **TRP**: transient receptor potential
- **TRPV1**: transient receptor potential vanilloid subfamily 1
- **SiRT-1**: sirtuin-1
- **PPAR**: peroxisome proliferator activated receptor
- **PGC-1α**: PPARγ coactivator 1α
- **PRDM-16**: PR domain 16 containing protein
- **BMP8b**: bone morphogenetic protein 8b
- **UCP-1**: uncoupling protein 1
- **CaMKKβ**: Ca$^{2+}$/calmodulin-dependent protein kinase kinase β
- **CaMKII**: Ca$^{2+}$/calmodulin dependent protein kinase II
- **AMPK**: 5'-adenosine monophosphate activated kinase
- **WAT**: white adipose tissue
BAT  brown adipose tissue
LD50  lethal dose 50

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