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Genetic Influence on Capsaicin Tolerance: Precision Nutrition Implications for Obesity Handling

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Capsaicin tolerance · Genetics · Polymorphism · Obesity · Precision nutrition

Abstract
Introduction: It has been suggested that capsaicin (CAP), a major pungent component in chili peppers, can be used as an anti-obesity ingredient due to effects on energy metabolism, but evidence is not consistent. Genetics may account for differences in CAP tolerance and its impact on adiposity status. The aim of this study was to systematically review current evidence concerning the role of genetic polymorphisms influencing CAP tolerance. ***Methods:*** The present systematic review analyzed and synthesized available evidence concerning associations between genetic polymorphisms and CAP tolerance following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) guidelines. Databases such as PubMed/MEDLINE, Cochrane, Scopus, Google Scholar, SciELO, and LILACS were screened. Out of 228 publications identified, only 6 meet inclusion criteria and were finally included in the final report. ***Results:*** Overall, a total of 28 single nucleotide polymorphisms were associated with several CAP tolerance traits including sensitivity to burning/stinging, heat pain, and cough reactions, and detection of bitter taste thresholds. These genetic variants were located within 6 genes involved in key physiological processes such synthesis of tetrahydrobiopterin and nitric oxide production (*GCH1*), CAP uptake and transduction of thermal stimuli (*TRPV1*), and bitter taste perception (*TAS2R38*, *TAS2R3*, *TAS2R4*, and *TAS2R5*). ***Conclusion:*** There is evidence about the influence of genetic polymorphisms on CAP tolerance by affecting nociceptive signaling, CAP binding, and bitter tasting. This knowledge may facilitate the design and implementation of innovative CAP-based nutrigenetic strategies for a more precise clinical management of obesity.

Introduction

Obesity is one of the most important challenges in health systems, affecting more than 650 million adults and approximately 340 million children and adolescents worldwide [1]. Obesity is a complex and multifactorial metabolic disease, which is associated with an increased risk of many adverse medical conditions including type 2 diabetes, cardiovascular events, liver damage, and some

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types of malignancies [2]. In consequence, these obesity-related chronic diseases globally cause about 5.0 million deaths, with higher rates in males than in females [3]. In fact, obesity also increase morbidity and disability, representing a significant economic and social burden to most populations in terms of cost-of-illness and health-related quality of life [4].

Lifestyle modification (diet and exercise) continues to be the cornerstone for primary obesity treatment [5]. Moreover, natural bioactive food compounds have been explored for their anti-obesity properties [6]. In this regard, it has been postulated that capsaicin (CAP), a major capsaicinoid active component in chili peppers responsible for pungent flavor, can be used efficiently as an anti-obesity ingredient [7]. Accordingly, a systematic review of clinical trials evidenced that daily consumption of capsaicinoids may contribute to weight management via reductions in appetite and energy intake, although a high heterogeneity was found [8]. In addition, a meta-analysis of clinical trials suggested that CAP supplementation may have modest effects in weight loss in overweight or obese individuals, but more clinical investigation is recommended to confirm these findings [9].

Epidemiological studies have analyzed relationships between chili intake and obesity prevalence, with contradictory results. On the one hand, chili consumption was reported to be inversely associated with the risk of developing overweight/obesity in Chinese adults [10]. On the other hand, investigations in Asian populations support positive associations between the consumption of chili and spicy foods with general [11] and abdominal obesity levels [12–14]. Also, a recent study in Mexican individuals suggested positive associations between dietary CAP intake and markers of body adiposity and fatty liver [15]. These findings may be related to geographic and environmental differences between populations influencing food intake and behavior but also to intrinsic factors affecting CAP metabolism and energy homeostasis, including genetics. Indeed, investigating the genetic influence on CAP use may explain, at least in part, some of the inconsistencies among observational studies relating CAP to risk of obesity. Furthermore, because the mechanism of action is not presently fully understood, additional research is needed to clarify if the putative effects of CAP on adiposity are related to metabolic or eating behavior features.

The aim of this article was to systematically review current evidence concerning the role of genetic polymorphisms influencing CAP tolerance. This information may lead to the design of genotype-based nutritional strategies for obesity management based on precise CAP consumption.

Methods

Search Strategy and Eligibility Criteria

The present systematic review analyzed and synthesized available evidence concerning associations between genetic polymorphisms and CAP tolerance, with no restrictions in year of publication. Methodological procedures were performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) guidelines [16]. Databases such as PubMed/MEDLINE, Cochrane, Scopus, Google Scholar, SciELO, and LILACS were screened. Reference lists of review articles were also scrutinized. Publications written only in English language were included. The search strategy included the following Medical Subject Headings (MeSH) terms: "capsaicin" OR "capsicum" OR "capsiate" OR "capsaicin tolerance" OR "capsaicin sensitivity" OR "capsaicin metabolism" OR "chili hotness" OR "chili pepper" OR "hot pepper" AND "genetic variant" OR "gene" OR "genomic" OR "polymorphism". Inclusion criteria comprised any type of study (observational, cross-sectional, cohort, case-control, clinical trials), available in full text, involving healthy subjects, children and adults, that evaluated the consumption of chili in the diet or the use of any method (oral or topical) of CAP use and that determined any genetic variant. Studies published as summaries or unpublished data, duplicate documents, animal or in vitro studies, languages other than English, review articles and meta-analysis were excluded. The screening was replicated at different times to guarantee reproducibility, and four researchers (ORL, YMA, AASN, and JRCM) performed independently the research. For the analysis and synthesis of the articles, a consensus of researchers (YMA, AASN, and ORL) was carried out to evaluate the quality and eligibility of each study according to the title and summary. Papers that meet the criteria from the selection phase were used in the data extraction phase.

Data Extraction

Overall, a total of 228 publications were identified: PubMed (n = 39), Scopus (n = 48), Cochrane (n = 13), Google scholar (n = 41), LILACS (n = 9), SciELO (n = 65), and reference lists of all relevant articles (n = 13). After deleting the duplicates (n = 9), the summaries of the remaining articles were examined (n = 200). Studies that did not meet the inclusion criteria (n = 187) were eliminated, resulting in 13 articles for full-text assessment for eligibility. Of these, 7 were further excluded. Finally, 6 articles were finally included in the present review (Fig. 1).

Results

According to selected studies, it was found that some genetic polymorphisms have an effect on CAP tolerance. The methodological details of the selected studies are summarized (Table 1). All included studies had a cross-

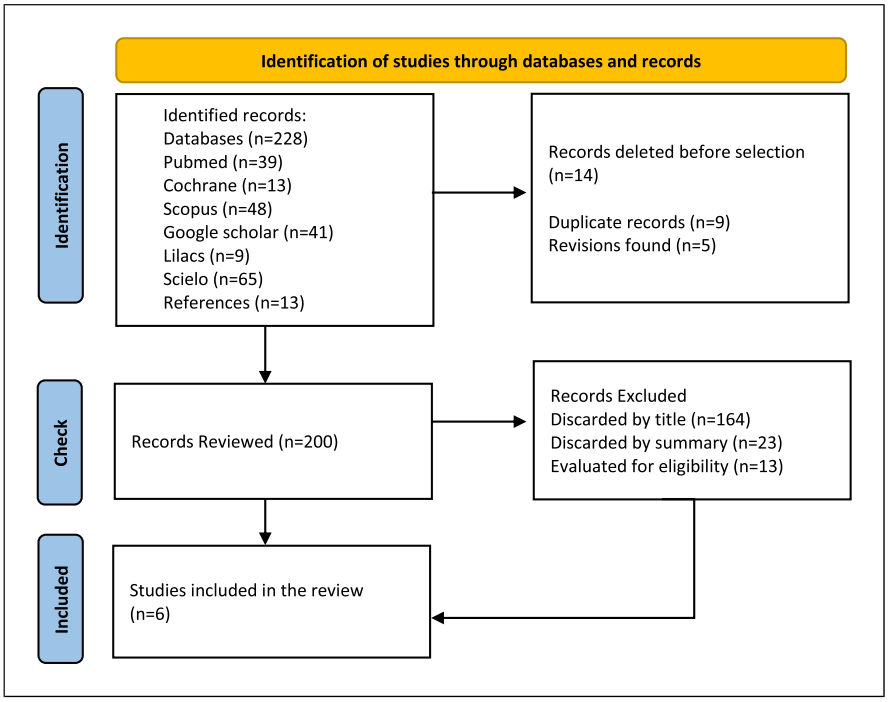

Fig. 1. PRISMA flow diagram summarizing the selection of papers included in this systematic review.

sectional design, and populations screened were heterogeneous, including Asians, Europeans, African, and Americans.

Overall, a total of 28 single nucleotide polymorphisms (SNPs) were associated with CAP tolerance. These genetic variants were located within 6 genes involved in key physiological processes such synthesis of tetrahydrobiopterin (BH4) and nitric oxide production (*GCH1*), CAP uptake and transduction of thermal stimuli (*TRPV1*), and bitter taste perception (*TAS2R38*, *TAS2R3*, *TAS2R4*, and *TAS2R5*). SNPs were distributed as follows: *GCH1* ($n = 3$), *TRPV1* ($n = 18$), *TAS2R38* ($n = 3$), *TAS2R3* ($n = 1$), *TAS2R4* ($n = 1$), and *TAS2R5* ($n = 2$). The main tests that were performed to measure tolerance to CAP were sensitivity to burning/stinging, heat pain, and cough reactions, and detection of bitter taste thresholds (Table 1).

For instance, it was analyzed the association of SNPs within the *GCH1* gene and pain ratings induced by topical application of CAP in 39 healthy participants. Tests revealed that pain intensity was higher in rs4411417 T/T and C/T, rs3783641 T/T, and rs752688 C/C genotype carriers after CAP administration [17].

Moreover, it was investigated the effect of the *TRPV1*-variant rs8065080 (1911A>G, I585V) on thermal sensitivity in 25 healthy subjects [18]. Of note, GG genotype carriers experienced less CAP-induced warm hypoesthesia in warm-detection and less CAP-induced heat pain sensitivity, suggesting an altered channel function in this genetic profile [18]. This same variant was tested to influence CAP cough challenge sensitivity in men, where a diminished capsaicin sensitivity was due to the *TRPV1*-V585 mutation, as corroborated after in vitro assays [19].

Of note, four combined *TRPV1* SNPs, 315M (rs222747), 585I (rs8065080), 469I (rs224534), and 91S (rs222749) explained higher cough sensitivity to a CAP challenge in healthy subjects [20]. Besides, higher burning pain sensitivity to CAP was associated to the following *TRPV1* SNPs: 2193 CT (rs460716), 14727 CG, 17775 CG (rs161385), 30580 AG (rs57716901)/30599 TG (rs61387317) haplotype, and 43524 TT + TG (rs4790523) in Japanese adults [21]. In addition, higher oral CAP sensitivity was related to the following *TRPV1* variants: 19274 GA, 21003 TT/21682 TT/24752 AA haplotype, 30580 AA/30599 TT haplotype, 33554 GG, 33605 AA, 43524 TT, 37280 TT, and 39341 TT in this same population [21].

Furthermore, variability in perceived bitterness of CAP was significantly associated with *TAS2R38* and *TAS2R3/4/5* diplotypes [22]. Thus, PAV homozygotes for the *TAS2R38* gene perceived greater bitterness from CAP on circumvallate papillae, compared to heterozygotes and AVI homozygotes. Similarly, CCCAGT homozygotes of *TAS2R3/4/5* diplotypes rated the greatest bitterness of CAP, compared to heterozygotes and TTGGAG homozygotes [22].

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Table 1. Summary of relevant studies analyzing the genetic influence on CAP tolerance

Study design	Population	Gene	Gene function	Polymorphism	Methodology	Results	Reference
CS	Healthy young adults (European Americans, Africans, and Asians), *n* = 39	*GCH1*	Amino acid metabolism and neurotransmitter production	rs4411417 (C/T) rs3783541 (T/A) rs7526887 (C/T)	CAP-induced pain CAP-induced pain stimulus	↓ Pain intensity in rs4411417 T/T and C/T, rs3783641 T/T, and rs752688 C/C ↓ Pain at 90 min in rs4411417 T/T, rs3783541 T/T, and rs7526887 C/C	[17]
CS	Healthy Germans, *n* = 25	*TRPV1*	CAP receptor and transducer of thermal stimuli	rs8065080 (A/G)	Pain/heat detection Patch (infusion) Laser doppler (magnitude)	↑ Pain onset time in AA/AG ↑ Sensitivity to the pain for heat in GG ↓ Heat detection in GG	[18]
CS	Europeans, *n* = 17	*TRPV1*	CAP receptor and transducer of thermal stimuli	rs8065080 (I585V)	Cough sensitivity to CAP Concentration of CAP causing 2 or 5 coughs	↓ Cough sensitivity to CAP in TRPV1-V585	[19]
CS	Healthy Italians, *n* = 20	*TRPV1*	Capsaicin receptor and transducer of thermal stimuli	rs222747 (I315M) rs8065080 (I585V) rs224534 (T469I) rs222749 (P91S)	Cough sensitivity to CAP Unique CAP breaths with dosimeter	↑ Cough sensitivity to CAP in 315 M, 585I, 469I and 91S combined	[20]
CS	Japanese, *n* = 26	*TRPV1*	CAP receptor and transducer of thermal stimuli	2193 (rs460716 C/T), 14727 (C/G), 17775 (rs161385 C/G), 30580 (rs57716901 A/G), 30599 (rs61387317 T/G), and 43524 (rs4790523 T/G)	Burning pain sensitivity Withdrawal latencies from the 48°C hot plate	↑ Burning pain sensitivity in 2193 CT, 14727 CG, 17775 CG, 30580 AG/30599 TG, 43524 TT+TG	[21]
CS	Japanese, *n* = 26	*TRPV1*	CAP receptor and transducer of thermal stimuli	19274 (rs117112057 G/A), 21003 (rs12936340 C/T), 21682 (rs7220415 G/T), 24752 (rs3744686 G/A), 30580 (rs57716901 A/G), 30599 (rs61387317 T/G), 33554 (rs8065080 G/A), 33605 (rs8078936 A/G), 37280 (rs57405156 T/C), 39341 (rs3826503 T/C), and 43524 (rs4790523 T/G)	Capsaicin sensitivity test CAP working solution in mouth in time intervals	Higher oral CAP sensitivity in 19274 GA, 21003 TT/21682 TT/24752 AA, 30580 AA/30599 TT, 33554 GG, 33605 AA, 43524 TT, 37280 TT, and 39341 TT	[21]

Table 1 (continued)

Study design	Population	Gene	Gene function	Polymorphism	Methodology	Results	Reference
CS	Caucasians, Asians, and African-Americans, $n = 106$	*TAS2R38*	Bitter taste perception	rs713598 (A49P) rs1726866 (V262A) rs10246939 (I296V)	CAP-impregnated swabs	↑ Bitterness in PAV homozygotes	[22]
CS	Caucasians, Asians, and African-Americans, $n = 106$	*TAS2R3*, *TAS2R4*, and *TAS2R5*	Bitter taste perception	*TAS2R3* (rs765007 C/T), *TAS2R4* (rs2234001 G/C), and *TAS2R5* (rs2234012 A/G and rs2227264 G/T)	CAP-impregnated swabs	↑ Bitterness in CCCAGT diplotype homozygotes	[22]

CAP, capsaicin; SNP, single-nucleotide polymorphisms; CS, cross sectional study.

Discussion

The results of this systematic review evidence the influence of some genetic polymorphisms on CAP tolerance traits, providing a better understanding on the individual preferences in its consumption and its impact on health. These variants were located in or near genes such as *GCH1*, *TRPV1*, *TAS2R38*, *TAS2R3*, *TAS2R4*, and *TAS2R5*, which regulate key biological/physiological processes.

GCH1, a member of the GTP cyclohydrolase family, participates in the enzymatic conversion of GTP into 7,8-dihydroneopterin triphosphate in the biosynthesis of tetrahydrobiopterin (BH4). The main function of BH4 is regulation of monoamine and nitric oxide production, which are implicated in nociceptive signaling [23]. Indeed, alterations in BH4 metabolism have been implicated in several pathological conditions including chronic pain [24]. Indeed, experimental inhibition of BH4 synthesis produces analgesic effects and attenuates neuropathic and inflammatory pain, whereas BH4 administration may exacerbates pain [25]. However, evidence supports that BH4 plays multiple roles in the cardiovascular, immune, nervous and endocrine systems via mitochondrial regulation, energy metabolism, antioxidant resistance of cells against stressful conditions and toxic pathways that may result in cell death, and protection from sustained inflammation, with implications in cardiovascular and metabolic diseases [26, 27].

TRPV1 is a nonselective cation channel, member of the vanilloid TRP family with high expression in sensory neurons, and a significant permeability to large polyvalent cations, calcium, and protons [28]. Although it is activated by numerous stimuli (i.e., heat, voltage, vanilloids, lipids, and protons/cations), CAP-induced TRPV1 intracellular signaling induce the depolarization of nociceptive neurons, leading to action potential firing and ultimately the sensation of spiciness [29]. TRPV1 (known as the specific CAP receptor) plays an essential role in the onset and progression of the burning pain sensation associated with inflammation in peripheral tissues, but it is additionally involved in a wide range of non-pain-related physiological processes including the maintenance of body and cell homeostasis and energy metabolism [30]. Thus, besides involvement in pathological inflammatory conditions, cancer and immunity disorders [31], TRPV1 channel has been also associated to the regulation of aging-associated weight gain and glucose tolerance, being relevant in diabetes prevention and weight control [32].

Furthermore, TAS2R38, TAS2R3, TAS2R4, and TAS2R5 belong to the specific class of G-protein coupled receptors (TAS2Rs or T2Rs) responsible for perceiving bitter taste in mammals [33]. Of note, it has been demonstrated that pure CAP elicit low levels of bitterness in some individuals but not

in others [34, 35]. T2Rs are located in taste buds of the tongue, palate and pharynx lie as well as in extraoral tissues including bronchial smooth muscle and chemosensory cells in gut, where they detect bitter chemicals in foods and other agonist substances [36]. When stimulated by bitter compounds, TA2Rs trigger a transduction cascade resulting in depolarization of the receptor cell and producing a signal conveyed to the central nervous system for sense processing [37]. Variation in bitter taste sensitivity may influence individual preferences for foods with bitter sensory qualities (i.e., cruciferous vegetables) and consequently impact health status [38]. In particular, T2Rs activation can influence appetite and body weight control, identifying T2Rs as promising targets for the treatment of obesity [39]. However, it has not been suggested that CAP bitterness is a barrier to chili intake, given that the amount of burn is much greater [40].

Obesity management remains an important challenge in clinical care and health systems. Due to beneficial properties on energy balance, CAP administration via supplementation or through chili intake has been postulated as a strategy for obesity control. However, experimental and epidemiological evidence reveal conflicting results, limiting the use of CAP as a potential anti-obesity nutritional therapy. Here, genetic variants affecting CAP tolerance are summarized, which may help to explain the heterogeneity in the effects of CAP on appetite and adiposity outcomes, but also emphasize the need of personalize the consumption of CAP for obesity handling. Moreover, this information provides a better picture in the study of CAP metabolism and contribute to a better understanding of the preferences in its consumption among individuals. However, given limited evidence in humans so far, it is necessary to conduct more clinical studies that explore the anti-obesity effects of CAP and its relationship with the genetic make-up. In addition to SNPs, other structural variants (i.e., genome insertions/deletions, copy number variants, and tandem repeats) need to be further explored for putative associations with CAP metabolism. Furthermore, the analysis of other populations is required, especially in those anciently exposed to CAP trough chili consumption such as Amerindians in Mexico and other Latin American countries with traditional food cultures.

Conclusion

The present systematic review supports the influence of genetic polymorphisms on CAP tolerance by affecting nociceptive signaling, CAP binding, and bitter tasting. This knowledge may facilitate the design of CAP-based nutrigenetic strategies for a more precise clinical obesity approach.

Statement of Ethics

A statement of ethics is not applicable because this study is based exclusively on published literature. Consent to participate statement is not applicable because this study is based exclusively on published literature.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

O.R.-L. conceived the study. O.R.-L. and Y.M.-A. wrote the manuscript. O.R.-L., Y.M.-A., A.A.S.-N., and J.R.C.-M. systematically searched bibliography and critically reviewed the document. All authors approved the final version of the manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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