Original Article

Possible Effects of Capsaicin (Chili Pepper) on the Oral Health

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Abstract

Background: Capsaicin binds the TRPV1 (transient receptor potential vanilloid), desensitizing the pain fibers that become insensitive to nociceptive stimuli. For this fact that the capsaicin has antipain and antiinflammatory properties, few studies verify possible harmful effects, especially with its use in high amounts. The aim of this study is to check salivary nitric oxide (NO) and malondialdehyde (MDA) as indicators of its possible oral health alterations. **Methods:** The protocol calls for twelve volunteers to eat 20 g of sausage with a high content of chili pepper and capsaicin. The study analyzes their salivary concentration of NO and MDA and in control group, 2 min, 1 h, and 1.5 h after ingestion. The U-Mann Whitney Calculator Test statistically analyzes these results. **Results:** Immediately after eating, there is a significant increase of NO and MDA vs control: *P* value is 0.03752 and 0.03236, respectively. The values of NO and MDA vs control remain higher after 1 h: *P* value is 0.04036 and 0.0466, respectively, to return to normality after 1.5 h. **Discussion:** This study shows that capsaicin increases the simultaneous production of MDA and NO. It is possible to hypothesize that MDA derives mainly from the inflammatory process up-regulated by COX-2, generated by capsaicin. We hypothesize instead that the excess of capsaicin inhibits and reduces the number of TRPV1, which produces an excess of NO and generates nitrosative stress. NO reacts with O_2 to form hydroxyl radicals (OH) and H_2O, or with superoxide anions to form MDA. **Conclusions:** The results of this study clearly show that the use not necessarily excessive of chili leads to developing an inflammatory process.

Keywords: *Capsaicin, food, free radicals, mouth, nitric oxide*

Introduction

Among the foremost necessary aspects of the lifetime of a nation, very important is to conserve on traditions, and among these, those associated with feeding habits. Many of these traditions remain real and necessary even today: This is attributable to the fact that eating particular foods has allowed several people to survive and maybe to have a larger physical performance in the time (fitness). The use of spices or foods like chili is a valid example, because in many countries this permitted the conservation of the food. In other several conditions, its use has the properties of mask the bad taste of some foods that were and maybe still are the few ones accessible in some countries. However, the use of spices cannot only be thought about healthy or indispensable, and in this study, we wish to debate the potential adverse effects associated with the use of chili. More precisely, we studied the effects of capsaicin (8-methyl-N-vanillyl-6-noneamide) on the oral cavity. Capsaicin is an organic compound found in plants of the Capsicum genus as chili pepper. This plant cultivated in tropical America has up to 1.5% of Capsaicin.[1] This chemical compound has several different helpful properties even though some don't seem sufficiently scientifically verified and despite this, it is a vital part of several supplements. Of explicit interest is the topical application of capsaicin on the inflammatory process of neurological origin.[2] Capsaicin is a powerful agonist of TRPV1 (potential transient vanilloid receptor potential): These receptors in a particle unleash through membrane channels expressed primarily at the somatic cell level, and in other different forms of tissues. Multiple stimuli, endogenous and exogenous, such as chemicals (resiniferatoxin, anandamide), mediators of inflammatory processes, acidity, temperature, and pH $\leq$ 5, activate this kind of receptors. The pain receptors are proteins that have loci specific to the motorial molecules and have spatial conformations to let to bind only capsaicin. Once capsaicin binds one among these receptors, it opens the channel that releases ions (Ca ++2), triggering successively the

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discharge of neurotransmitters that send signals to the brain and the typical feeling of the native burning, followed by an analgesic result that lasts over time. For this fact, the pain fibers become insensitive to nociceptive stimuli of any kind. The inability to painful stimuli is not solely due to a decrement of receptors, because the capsaicin also produces a complex condition called "defunctionalization" that consists of structural changes of fibers.[3] For these reasons, capsaicin would seem to own pain-relieving properties and would even be helpful against inflammation and to manage many inflammatory diseases like arthritis. Unlike this set of scientifically valid information, there are few studies that on an epidemiological basis and on animal experiments may show the chance that capsaicin could inhibit the co-cancerogenesis process in some carcinoma.[4,5] However, the influence as an inhibitor of cancer of the foods containing capsaicin or vegetables, on patients with carcinoma remains unknown for the most part. In any case instead, there is little doubt that capsaicin promotes on the far side the intense and acute burning mouth process, it will be assumed that the chronic use of chili conjointly involves a principle of inflammation of the animal tissue. The aim of this study is to verify and explain this development and analyze the secretion concentrations of gas (NO) and MDA.

Methods

Twelve volunteers, six men and six women with an average age of 28 years, eat, in about 4 min, 20 g of a particular food called "nduja," spicy sausage typical of the Calabria country, which can also be eaten by smearing the same on bread. The "nduja" has on average 17 mg of capsaicin/gram. The volunteers in this study ingest a high dose of capsaicin, about 100 mg. Usually, the method to prepare the "nduja" is to mix two parts of meat with one part of Calabria chili pepper that has 500 Scoville units, very high value, but extremely lower compared to other types of chili peppers known exceed 2,000,000 Scoville units. The concentrations that we found of MDA and NO are the values relative of three saliva samples of both groups: the first represents the sample on the 2 min after the meal, the second after 1 h, and the third after 1.5 h. In this study, we analyzed the saliva samples from volunteers who have been after careful analysis of anamnesis about the health of the oral cavity to rule out possible diseases that could affect the characteristics of a normal salivary composition excluding that arising from regular cell metabolism. We examined samples of saliva represented what all salivary glands produce, and this is called "the whole saliva." This saliva when secreted under resting conditions is called the "unstimulated saliva" and collected between 10 AM and 12:30 PM. The thiobarbituric acid test (TBA) determinates the MDA concentration, while the Griess method determinates the NO concentration. The TBA concerns the reaction the thiobarbituric acid that reacts with MDA produced when hydroperoxides in lipid systems decompose. The result is a red-collared chromophore compound with a peak absorption at 532 nm. The color's intensity is proportional to the aldehydes' concentration in the sample. This collared complex results from the condensation reaction of two moles of thiobarbituric acid with a mole of MDA, under the joint effect of the medium, temperature, and pH. Many direct and indirect methods can measure them. Nitric oxide concentration, but the short half-live and low concentrations of NO *in-vivo* cuts the value of these methods for the evaluation of biological samples. In addition, these rules are generally unsuitable for the clinical laboratory due to instrumentation requirements and inexpedience in processing many of the samples. The measure of the stable metabolites, in particular, nitrite and nitrate, cuts the difficulties inherent to the quantification of NO. The simplest and most often applied method is colorimetric detection with Griess reagent Nitric oxide (NO) analysis. The Mann-Whitney U Test is the method for the statistical analysis of the values determined in the two groups, which is a nonparametric test that allows comparing two groups or conditions or treatments, without assuming that values are normally distributed.

Results

The values of Table 1 show the MDA concentrations, respectively, immediately after the consumption of 20 g of "Anduia," after 1 h, and after 1.5 h.

The values of Table 2 show the NO concentrations, respectively, immediately after the consumption of 20 g of "Anduia," after 1 h, and after 1.5 h.

1-Result for MDA concentrations 1 min after the eating of Anduia vs Control. The U-value is 13. The critical value of U at P <.05 is 37. Therefore, the result is significant at P <.05. The z-score is 3.3775. The P value is. 00072.

2-Result for MDA concentrations 1 h after the eating of Anduia vs Control. The U-value is 36. The critical value of U at P <.05 is 37. Therefore, the result is significant at P <.05. The z-score is 2.04959. The P value is. 04036.

3-Result for MDA concentrations 1.5 h after the eating of Anduia vs Control. The U-value is 64.5. The critical value of U at P <.05 is 37. Therefore, the result is not significant at P <.05. The z-score is -0.40415.

4-Result for NO concentration 1 min after the eating of Anduia vs Control. The U-value is 15.5. The critical value of U at P <.05 is 23. Therefore, the result is significant at P <.05. The z-score is 2.57016. The P value is. 01016.

5-Result for NO concentration 1 h after the eating of Anduia vs Control. The U-value is 10. The critical value of U at P <.05 is 13. Therefore, the result is significant at P <.05. The z-score is 2.25795. The P value is. 02382.

6-Result for NO concentrations 1.5 h after the eating of Anduia vs Control. The U-value is 55. The critical value of U at P <.05 is 30. Therefore, the result is not significant at

Table 1: Salivary MDA concentrations

Patient Groups					Control Group		
Sex	Age	MDA conc 1 min (nM/ml)	MDA conc 1 h (nM/ml)	MDA conc 1.5 h (nM/ml)	Sex	Age	MDA conc (nM/ml)
F	22	3.6	3.1	1.4	F	21	1.5
F	29	2.8	2.4	1.9	F	29	1.6
F	33	3.0	2.6	2.0	F	36	2.5
F	34	3.2	2.7	1.8	F	33	1.8
F	27	3.6	3.1	3.1	F	30	3.1
F	30	3.4	3.0	1.6	F	31	1.8
M	30	2.8	2.4	3.0	M	31	3.1
M	21	2.6	2.0	2.0	M	21	2.0
M	23	3.7	3.0	1.4	M	23	1.4
M	29	3.8	3.0	2.0	M	27	2.3
M	34	3.9	3.4	2.0	M	35	2.7
M	35	4.3	3.9	3.1	M	38	3.1

Table 2: Salivary NO concentration

Patient Groups					Control Group		
Sex	Age	NO conc 1 min* (μM/ml)	NO conc 1 h (μM/ml)	NO conc 1.5 h (μM/ml)	Sex	Age	NO conc 1 h (μM/ml)
F	22	89.5	88.5	70.5	F	21	69.5
F	29	83.0	83.0	72.0	F	29	73.0
F	33	82.0	81.0	71.0	F	36	70.0
F	34	75.7	74.7	70.7	F	33	68.7
F	27	82.3	82.5	72.5	F	30	73.3
F	30	86.0	84.9	74.9	F	31	76.0
M	30	83.3	80.9	80.9	M	31	753
M	21	83.0	80.0	80.0	M	21	78.0
M	23	84.5	84.5	77.5	M	23	76.5
M	29	76.0	75.0	75.0	M	27	74.0
M	34	85.0	84.0	78.0	M	35	75.0
M	35	84.2	82.2	72.2	M	38	74.2

P <.05. The z-score is 0.32833. The P value is. 7414. The result is not significant at P <.05.

Discussion

This study shows that eating food sausage that has a high amount in chili pepper and in capsaicin promotes to produce a high amount of salivary MDA and NO in the consumer group. These salivary amounts have more high-level immediate after their consume: These values are statistically significant if compared to the control group. These results, expressed in Tables 1 and 2, show that are necessary two contemporary and different biochemical processes to increase the NO and MDA salivary concentrations, within at least 2 h of its consume. The goal of our study is to understand the possible biochemical pathways that promote high amounts of salivary MDA for its relationship with possible carcinogenic effects. Another aim is to understand this process in a relationship with the biochemical pathway that forms NO. The inflammatory process that capsaicin induces directly on the oral mucous membranes is certainly the first biochemical pathway to form the MDA. The conclusions of most recent studies that have analyzed the potential co-carcinogenic effects of the capsaicin's application to the skin of mice (4) show a significant increase in the levels of COX-2(cyclooxygenase-2) in mice treated with capsaicin and 12-O-tetradecanoyl phorbol-13-acetate (TPA) than in mice treated with TPA alone. The COX-2 is an inducible enzyme, present during the inflammatory processes of the tissues, and only in a few numbers of cell types. The COX-2 controls the inflammatory process, with an up-regulated mechanism, but the principal conclusion is that the inflammatory processes are a synonym of possible mechanisms to promote cancer. This biological event promotes as a first step the mechanism to lipid peroxidation to produce MDA. In our study, the contact of capsaicin to oral mucosa causes a similar inflammatory process, or more precisely a neurogenic inflammation. When we apply the capsaicin to the oral mucosa, it induces a nociceptive effect of the oral epithelium, triggered by the release of neuropeptides as the Substance P[6] from the cutaneous sensory nerve endings.[7,8] The *P* substance acts upon micro vascularization, has vasodilatory effects, increases vascular permeability, and favors the release of proinflammatory cytokines.[9] Another important result of capsaicin's

nociceptive effects is that the neuropeptides induce mast cell degranulation and synthesis of pro-inflammatory cytokines.[8] The mast cell mediators, in turn, activate nociceptors and further amplify the release of neuropeptides from the sensory nerves. All inflammatory processes are certainly indicators of oxidative stress and contemporary to it. Anyway, the data in Table 2 show that also the NO production is representative of a response to these inflammatory processes. We can see a close correlation between the increase and the later decrease in salivary MDA, parallel to the concentrations of salivary NO. We assume for this fact that capsaicin involves not only the receptor's desensitization but also produces a more complex condition called "defunctionalization" which consists of functional and structural changes of the nerve fibers. The partial response to an obvious inflammatory process is the NO production which results from the fact that part of the capsaicin interacts with the part of the oral epithelium, where the TRPV1 receptors are defunctionalized.[10] In general, the main biochemical stage to form NO starts from arginine which, with an oxidation reaction catalyzed by the enzyme nitric oxide synthase (NOS), of a constituent or inducible type (I NOS II), produces NO. Chemical mediators of inflammation such as TNF a and IL-1 form significant amounts of NO for many long periods, as well happens as from the endotoxin of negative gram bacteria. Generally, the NO has antiinflammatory properties because it inhibits the synthesis and expression of cytokines and adhesion molecules that attract inflammatory molecules. To inhibit this process, the nuclear transcription factor NFkB that binds to the promoter region of the gene that encodes for inflammatory proteins acts as a mediator effect NO is cytoprotective, because it blocks the respiratory chain mitochondria to form the harmful reactive species of oxygen (ROS). Generally also if the NO by its nature is a compound that from the point of view of chemical stability, the same is perennially in an intermediate state of oxidation, so it is able to oxidize and cut the compounds it comes into contact with the same. Hence, in some conditions, NO may have cytotoxic effects.[11,12] Many cytotoxic effects depend on important metal proteins inactivation, because NO can react with the ferrous heme group (Fe2+),[13] in hemoglobin, and in guanylate cyclase, with the iron-sulfur centers with free cysteines such as aconitase,[14] with the -SH groups of glutathione, and finally with copper, e.g., cytochrome oxidase. The cytotoxic effects of NO are comparable to those induced by other oxidizing agents.

Conclusions

The results of this study clearly show that the use not necessarily excessive of chili leads to developing an inflammatory process. This process also produces a high number of free radicals, and persists for 2 h, after which the situation returns to normal. It is clear that it is difficult to assess the long-term effects of taking capsaicin with food although the results of this study must caution to the use of the high intake of spices with a high content of spiciness. The results of this study are in partial contrast with other research: These data, in fact, show that maybe some controversies related to the consumption or topical application of capsaicin, or even and especially the use through food. It is clear that the further development of studies such as ours must aim to evaluate the effects of capsaicin at other organs such as the esophagus. Another possible avenue of investigation must execute the epidemiological studies better controlled to assess the safety and effectiveness of the use of capsaicin.

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Conflicts of interest

There are no conflicts of interest.

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