



## Review

# Use of capsaicin as a model in the study of migraine: a literature review

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## Abstract

Capsaicin is able to induce mast cell degranulation, an event probably related to the pathophysiology of a migraine attack. The present review study aimed to address the mechanisms of action of capsaicin and other chemical inducers in mast cell degranulation and an interaction of nerves and events that happen in the dura mater with the activation of mast cells. A survey was carried out in the literature, from 1980 to 2019, in different databases, using the following terms: capsaicin, mast cell and dura mater. 36 articles were selected for this review. Studies indicate that the main mechanisms of action of capsaicin are chemical induction through the activation of TRPV1 channels, allowing calcium influx into neurons in the trigeminal ganglion of the dura mater, activating mast cell degranulation, releasing pro-inflammatory (e.g., histamine, oxide nitric) and vasoactive (e.g., CGRP and substance P) substances. Therefore, the use of capsaicin may be a tool to be used in an animal model to better understand the pathophysiology of migraine.

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## Introduction

The mast cells are present in the proximity of sensory nerve fibers in the rat dura mater.<sup>1</sup> There is an interaction between mast cells with C fibers in the dura mater.<sup>2</sup> Vasodilation, plasma leakage and degranulation of mast cells contribute to the release of pro-inflammatory substances in the dura mater, probably related to migraine attacks.<sup>3-5</sup> The mast cell degranulation has been suggested as an important element of neurogenic inflammation, as mast cells exclusively release histamine when activated by the release of Calcitonin gene-related peptide (CGRP) at the trigeminal terminals.<sup>6-8</sup> Histamine mediating CGRP receptors are likely to be located in mast cells.<sup>9-12</sup> In addition to CGRP, histamine also interacts with increased production of nitric oxide (NO) in the mast cells.<sup>13-16</sup> All three chemical mediators contribute to vasodilation and neurogenic inflammation.<sup>17</sup> Therefore, CGRP is able to release histamine and increase NO production from meningeal mast cells and act as a very potent vasodilator of intracranial arteries, occupying a prominent position in the nociceptive elements in the primary cascade of a headache attack.<sup>17</sup>

The capsaicin is one of the chemicals used in animal studies to activate the trigeminovascular system mimicking part of the migraine pathophysiological process and serving as an experimental model, as it is associated with the release of neuropeptides, through the opening of cationic channels that results in accumulation of intracellular calcium, and mast cell activation.<sup>18</sup> These mast cells, through vasoactive mediators, contribute to stimulation of the large cranial arteries resulting in neurogenic inflammation and this is essential for their involvement in primary headaches.<sup>19,21</sup> Thus, this review aims to deepen the knowledge about the mechanisms of action of capsaicin and other chemical inducers in the involvement of mast cell degranulation in a migraine attack.

## Methods

This review was conducted with articles that used capsaicin to activate mast cells, in addition to other chemical inducers that demonstrated interaction between the dura mater and mast cells. The search was carried out with articles published between the years 1980 and 2019. Articles from SciELO, U.S. National Library of Medicine and the National Institutes Health (PubMed) and Web of Science databases were evaluated. As search strategy, the following terms were used: "Capsaicin" and "mast cell" and "dura mater" selected in consultation with the Medical Subject Headings (MeSH). The inclusion criteria were experimental model studies in rats that described the mechanisms of action of chemical inducers,

including capsaicin. Initially, the titles and abstracts of the articles found were read. Then, the articles were read and, finally, an additional search was carried out that tracked reference lists of all identified articles.

## Results

Of the total 50 articles found, 36 were selected for this review.

## Discussion

Capsaicin in experimental animal models is used to induce inflammation via chemical stress that increase vascular permeability in the dura mater by activating mast cells caused by the release of neuropeptides.<sup>22,23</sup>

The transient potential of the cationic receptor of the V sub-family member 1 (TRPV1) also known as the capsaicin receptor, it's a channel that acts as a mediator to stress. After activation of these channels, they contribute to the opening of intracellular calcium and potassium output, leading to hyperpolarization of trigeminal neurons and vasodilation through the release of CGRP and substance P, neuromodulator that facilitates inflammatory processes. Thus, TRPV channels play vital roles in the vasculature and an important mediator for vascular responses.<sup>24,26</sup> Baylie e Brayden<sup>22</sup> demonstrated that stimulating actions increase the release of vasoactive peptides. Szolcsanyi<sup>23</sup> analyzed the depletion of sensory neurons by capsaicin and the relation of neuropeptides released in the analysis of the diameter of the cranial arteries, to verify whether there was dilation. Huang et al.<sup>27</sup> observe that chemical stimulation with capsaicin also influences the release of CGRP assessed immunohistochemically through the polyclonal antibody of rabbits.

The activation of mast cells by capsaicin leads to degranulation and the consequent release of pro-inflammatory substances (histamine and nitric oxide). Histamine increases CGRP levels released by C fiber neurons and consequently more numbers of degranulated mast cells, a positive feedback cycle, and nitric oxide contributes to controlling the viability of cranial arteries. In studies using capsaicin, it was observed that in neonates rats, chemical stimulation destroyed the peptidergic nerve endings, demonstrating that stresses in neonates do not induce mast cell degranulation.<sup>22,23</sup>

The stimulating action of capsaicin to increase the release of neuropeptides causes depletion of sensory neurons, releasing

CGRP causing destruction of peptidergic nerve endings in neonatal animals that do not have a consistent neural structure. Dimtriadou et al. (1991) used capsaicin (50mg/kg; 48 h) administered subcutaneously in rats and do not had statistical difference in mast cell degranulation of the dura mater. Years later, with higher doses of capsaicin (50 mg/kg, 1 day of life and 100 mg/kg, 3 days of life) there was a statistical difference in the degranulation of mast cells of the dura mater, due to the increase in the capsaicin dose.<sup>28,29</sup> Thus, neonates are not a good experimental model to mimic the pathophysiology of migraine, because they do not have a consistent and defined neural structure as in adult rats.

In studies with adult rats, capsaicin was able to induce a dose-response in the histamine release and consequent activation of mast cells, observing significant degranulation results.<sup>30</sup> As observed in another study that showed that foods containing capsaicin are able to suppress neuropeptides such as substance P that can cause the co-release of CGRP, since they are often located in the same neuron, thus activating the release of histamine in mast cells, mediating mast cell activation.<sup>31</sup> This connection of mast cells with sensory neurons in the dura mater has a bidirectional response, where it signals responses with the nerves in relation to the external environment and endogenous and exogenous substances and degranulation in response to dural signals for the body's immunity.<sup>32,33</sup>

In adult rats, it was also shown, through other inducers, as cholinergic agents (carbacol and nicotine); ovarian hormones and compound 48/80, a polymer that promotes histamine release, the percentage of degranulated mast cells in the dura mater and its relationship with migraine. It was observed that these chemical inducers had different mechanisms of action to activate mast cells, presenting significant results in the percentage of degranulation and in the pathophysiology of migraine.<sup>34</sup> In the study relating the ovarian hormones (estradiol and progesterone) to the density of mast cells in the dura mater and their potential role in headache, it is observed that the application of estrogen, but not progesterone, increases the density of mast cells.<sup>34,35</sup> In the study of differentiating neuropeptides with vasoactive potentials, PACAP-38 to PACAP-27, in the dura mater and the frequency of mast cell degranulation, it was found that the difference is not in the pituitary adenylate cyclase-activating polypeptide type I (PAC1) receptor but because PACAP38 has greater induction in mast cell degranulation by acting via phospholipase C, which presents enzymes that contribute to the opening of intracellular calcium.<sup>35</sup> And in the study of cholinergic agents in the activation of calcium channels sensitized by CGRP, there is a relationship that suggests nociceptive regulation of the meninges, providing firing to primary afferents assuming

that this is the source of the headache, causing a significant mast cell degranulation and inducing vasodilation in the dura mater.<sup>36</sup> Then, other stimulants have mechanisms of action that resemble capsaicin to degranulate mast cells and increase the levels of these three inflammatory mediators.

Thus, probably due to the actions of capsaicin, it is possible to study the pathophysiology of the migraine by mast cell degranulation. Mast cell degranulation was considered a fundamental element for migraine physiopathology, as activation and consequent degranulation increases the plasma levels of three chemical mediators (CGRP, histamine and nitric oxide) that are related to vasodilation. Capsaicin, with its neuron-stimulating action, opens calcium ion channels, leading to neuron hyperpolarization and the release of vasoactive neuropeptides, activating mast cells and causing vasodilation.

## Conclusion

The method of inducing mast cell degranulation by chemical activation of capsaicin, and other inducers, mimics the pathophysiological process of migraine by activating the trigeminovascular system and neurogenic inflammation.

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