



## Release of CGRP in vivo from rat dura mater: Influence of capsaicin and topiramate

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### Introduction

Migraine is a disease that stands out for its high prevalence with changes in the nervous system, abnormal levels of neurotransmitters, neuromodulators, and neuropeptides. The main mechanisms of action of capsaicin are chemical induction through the activation of TRPV1 channels, allowing calcium influx into neurons, activating mast cell degranulation, releasing pro-inflammatory (e.g., histamine, oxide nitric) and vasoactive (e.g., CGRP and substance P) substances. For treatment, classes of drugs are used to act on blood vessels and to prevent vasodilation, as well as depolarization of sensory fibers of the dura mater.

### Objectives

To better understand sterile inflammation after exposing the dura mater bilaterally, we created an experimental model to study mechanisms of action of topiramate and capsaicin in mast cell degranulation and release of CGRP in a rat skull preparation in vivo using anesthetized animals.

### Methods

Thirty-five Wistar rats were used, divided into two groups: (1) chronic topiramate (GTC) treated with 20 mg/kg/day, gavage/10 days, and (2) acute topiramate (GTA) in situ in the dura mater (10-3M). The animals were anesthetized and cranial windows between the coronal and lambda sutures in the hemispheres were performed with a drill to expose the dura mater bilaterally. 10-3M capsaicin was placed on the right side and synthetic interstitial fluid on the left side and exposed to contact for 10 minutes to a small cotton ball soaked with the respective solutions so that there is no leakage of the treatment, and posteriorly kept in the freezer (-20°C) for later quantification of CGRP. The percentage of degranulated mast cells was quantified after removal of the dura mater by staining it with toluidine blue. A commercial enzyme immunoassay quantified the release of CGRP from the cranial dura mater.

### Results

There was a greater amount of degranulated mast cells in the dura stimulated by capsaicin, females ( $18.43 \pm 0.03\%$  versus  $73.11 \pm 0.03\%$ ;  $p=0.001$ ) and males ( $27.21 \pm 0.01\%$  versus  $75.00 \pm 0.02\%$ ;  $p=0.001$ ). In the group treated with topiramate for 10 days, there were fewer cells degranulated by capsaicin ( $22.80 \pm 0.03\%$  versus  $77.00 \pm 0.03\%$ ,  $p=0.001$ ). Topiramate placed in situ concomitant with capsaicin also attenuated the mast cell degranulation process ( $35.74 \pm 0.04\%$  versus  $44.52 \pm 0.02\%$ ;  $p=0.001$ ). However, the release of CGRP induced by capsaicin was not significantly different compared to synthetic interstitial fluid.

### Conclusion

This study demonstrated that capsaicin is a method of chemical induction and stimulation of mast cells and that topiramate attenuates the effect of capsaicin. We did not see evidence for CGRP in this study because capsaicin did not stimulate CGRP release.

**Keywords:** Migraine, Pathophysiology, Topiramate, Capsaicin, CGRP, Rat.