Headache Medicine 2026, Supplement ▪ p-ISSN 2178-7468, e-ISSN 2763-6178

Headache Medicine

ID: 118

Intracellular CGRP signaling in migraine: preferential involvement of protein kinase A in trigeminal allodynia

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Introduction
Migraine is a disabling neurological disorder characterized by recurrent headache attacks associated with nausea, photophobia, and phonophobia. Among the mediators involved in its pathophysiology, calcitonin gene-related peptide (CGRP) is particularly relevant. CGRP is widely distributed throughout the trigeminal system, including the trigeminal ganglion, where it contributes to nociceptive sensitization. Activation of the canonical CGRP receptor triggers different intracellular signaling cascades, including the G s/AC/cAMP/PKA and Gαq11/PLC pathways. However, the specific contribution of these pathways to CGRP-induced sensitization processes remains unclear.

Objective
This study investigated the effects of the pharmacological blockade of protein kinase A (PKA) and protein kinase C (PKC) on nociceptive responses induced by CGRP in the trigeminal ganglion of male and female rats.

Methods
Adult Wistar rats were previously selected according to their baseline periorbital mechanical threshold, determined using von Frey filaments (0.04–8 g). The animals received H89 (a PKA inhibitor), BIM (a PKC inhibitor), or vehicle (saline), followed 15 minutes later by CGRP or vehicle administered into the trigeminal ganglion. The periorbital mechanical threshold was assessed for four hours after treatment. After 24 hours, the animals were exposed to bright light for one hour and reassessed at the same time points. All experimental procedures were approved by the Institutional Animal Care and Use Committee (CEUA) under protocol No. 1595.

Results
The results showed that CGRP significantly reduced the periorbital mechanical threshold in both male and female rats, indicating mechanical allodynia. Moreover, exposure to light on the following day reactivated mechanical allodynia in CGRP-treated animals, indicating photosensitivity. PKA blockade significantly reduced the CGRP-induced nociceptive response in both sexes but did not affect photosensitivity. In contrast, PKC inhibition did not prevent the development of CGRP-induced periorbital allodynia or photosensitivity in male or female rats.

Conclusion
The findings suggest that immediate CGRP-induced periorbital mechanical allodynia, but not photosensitivity, depends on activation of the G s/AC/cAMP/PKA pathway in the trigeminal ganglion of both male and female rats. These results contribute to understanding the cellular mechanisms involved in migraine headache and identifying potential cellular targets.

Keywords:
Headache
Migraine
Protein kinase A
Protein kinase C
Calcitonin gene-related peptide

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