Cephalalgia 2017 vol.37 N14, pages 1373-1383

Pro-nociceptive migraine mediator CGRP provides neuroprotection of sensory, cortical and cerebellar neurons via multi-kinase signaling

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Abstract

© 2016, © International Headache Society 2016. Background: Blocking the pro-nociceptive action of CGRP is one of the most promising approaches for migraine prophylaxis. The aim of this study was to explore a role for CGRP as a neuroprotective agent for central and peripheral neurons. Methods: The viability of isolated rat trigeminal, cortical and cerebellar neurons was tested by fluorescence vital assay. Engagement of Nrf2 target genes was analyzed by qPCR. The neuroprotective efficacy of CGRP in vivo was tested in mice using a permanent cerebral ischemia model. Results: CGRP prevented apoptosis induced by the amino acid homocysteine in all three distinct neuronal populations. Using a set of specific kinase inhibitors, we show the role of multi-kinase signaling pathways involving PKA and CaMKII in neuronal survival. Forskolin triggered a very similar signaling cascade, suggesting that cAMP is the main upstream trigger for multi-kinase neuroprotection. The specific CGRP antagonist BIBN4096 reduced cellular viability, lending further support to the proposed neuroprotective function of CGRP. Importantly, CGRP was neuroprotective against permanent ischemia in mice. Conclusion: Our data show an unexpected 'positive' role for the endogenous pro-nociceptive migraine mediator CGRP, suggesting more careful examination of migraine prophylaxis strategy based on CGRP antagonism although it should be noted that homocysteine induced apoptosis in primary neuronal cell culture might not necessarily reproduce all the features of cell loss in the living organism.

http://dx.doi.org/10.1177/0333102416681588

Keywords

CaMKII, cAMP, cerebellum, CGRP, cortex, ischemia, migraine, neuroprotection, trigeminal ganglion

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