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Differentiation of nerve fibers storing CGRP and CGRP receptors in the peripheral trigeminovascular system

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Background

The dura mater with the meningeal artery has since long been hypothesized to play an important role in migraine. It has been suggested that neuropeptides such as calcitonin gene-related peptide (CGRP) and substance P can activate dura mast cells leading to secretion of vasoactive, pro-inflammatory and neurosensitzing mediators, thereby contributing to migraine pathogenesis. Method: Immunofluorescence was used to study the detailed distribution of and its receptor components- calcitonin receptor-like receptor (CLR) and receptor activity modifying protein 1 (RAMP1)- in whole-mount rat dura mater, using a set of newly characterized antibodies. Their relation to each other, to mast cells, myelin, substance P, neuronal nitric oxide synthase (nNOS), pituitary adenylate cyclase-activating polypeptide (PACAP) and vasoactive intestinal peptide (VIP) were studied. In addition, we examined expression of CGRP and its receptor components in fresly isolated human dura vessels.

Results

CGRP expression was found in thin fibers, while CLR and RAMP1 were expressed in thicker fibers. Double-staining of CGRP and the receptor components showed no co-localization. CLR and RAMP1 expression were found in cells, co-localized with mast cell tryptase. Double-staining with CGRP and MBP showed no co-localization. CLR and RAMP1 immunoreactive fibers co-localized with MBP and NF160/200. Substance P fibers co-expressed CGRP. nNOS and VIP expression was very limited and these fibers were distinct from the CGRP positive fibers. Few PACAP immunoreactive fibers co-localized with CGRP. No expression of functional CGRP receptor was observed in human mast cells.

Conclusions

CGRP is expressed in un-myelinated fibers C-fibers. CLR and RAMP1 are instead expressed in myelinated fibers A-fibers. This supports the view that activation of C-fibers may locally cause release of CGRP, which could act on A-fibers, mast cells and vascular smooth muscle cells. Interestingly, CLR and RAMP1 expression was found in rat dura mast cells, however, human mast cells lack expression of functional CGRP receptor.

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