Cysteine-rich protein 2, a novel downstream effector of cGMP/cGMP-dependent protein kinase I-mediated persistent inflammatory pain.


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BACKGROUND: The cGMP/cGMP-dependent protein kinase I (cGKI) signaling pathway plays an important role in spinal nociceptive processing. However, downstream targets of cGKI in this context have not been identified to date.

OBJECTIVE: Using a yeast two-hybrid screen, we isolated cysteine-rich protein 2 (CRP2) as a novel cGKI interactor in the spinal cord. CRP2 is expressed in laminae I and II of the mouse spinal cord and is colocalized with cGKI, calcitonin gene-related peptide, and isolectin B4. Moreover, the majority of CRP2 mRNA-positive dorsal root ganglion (DRG) neurons express cGKI and peripherin. CRP2 is phosphorylated in a cGMP-dependent manner, and its expression increases in the spinal cord and in DRGs after noxious stimulation of a hindpaw.

METHODS: To elucidate the functional role of CRP2 in nociception, we analyzed mice with a targeted deletion of CRP2.

RESULTS: CRP2-deficient (CRP2-/-) mice demonstrate normal behavioral responses to acute nociception and after axonal injury of the sciatic nerve, but increased nociceptive behavior in models of inflammatory hyperalgesia compared with wild-type mice. Intrathecal administration of cGMP analogs increases the nociceptive behavior in wild-type but not in CRP2-/- mice, indicating that the presence of CRP2 is important for cGMP-mediated nociception.

CONCLUSION: These data suggest that CRP2 is a new downstream effector of cGKI-mediated spinal nociceptive processing and point to an inhibitory role of CRP2 in the generation of inflammatory pain.

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