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Cysteine-rich protein 2 is a downstream effector of cGMP-dependent protein kinase I in nociception

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The experience of pain is mediated by a specialized sensory system, the nociceptive system. There is considerable evidence that the cGMP/cGMP kinase I (cGKI) signaling pathway modulates the nociceptive processing within the spinal cord. However, downstream targets of cGKI in this context have not been identified to date. In this study we investigated whether cysteine-rich protein 2 (CRP2) is a downstream effector of cGKI in the spinal cord and is involved in nociceptive processing. Immunohistochemistry of the mouse spinal cord revealed that CRP2 is expressed in superficial laminae of the dorsal horn. CRP2 is colocalized with cGKI and with markers of primary afferent C fibers. Importantly, the majority of CRP2 mRNA-positive dorsal root ganglion (DRG) neurons express cGKI and CRP2 is phosphorylated in a cGMP-dependent manner. To elucidate the functional role of CRP2 in nociception, we investigated the nociceptive behavior of CRP2-deficient ($CRP2^{-/-}$) mice. Touch perception and acute thermal nociception were unaltered in $CRP2^{-/-}$ mice. However, $CRP2^{-/-}$ mice showed an increased nociceptive behavior in models of persistent pain as compared to wild type mice. Intrathecal administration of cGKI activating cGMP analogs increased the nociceptive behavior in wild type but not in $CRP2^{-/-}$ mice, indicating that the presence of CRP2 was essential for cGMP/cGKI-mediated nociception. These data indicate 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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