Sensitization of nociceptors by prostaglandin E₂-glycerol contributes to hyperalgesia in mice with sickle cell disease.

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Abstract

Pain is a characteristic feature of sickle cell disease (SCD), 1 of the most common inherited diseases. Patients may experience acute painful crises as well as chronic pain. In the Berkley transgenic murine model of SCD, HbSS-BERK mice express only human hemoglobin S. These mice share many features of SCD patients, including persistent inflammation and hyperalgesia. Cyclooxygenase-2 (COX-2) is elevated in skin, dorsal root ganglia (DRG), and spinal cord in HbSS-BERK mice. In addition to arachidonic acid, COX-2 oxidizes the endocannabinoid 2-arachidonoylglycerol (2-AG) to produce prostaglandin E₂ (PGE₂)-glycerol (PGE₂-G); PGE₂-G is known to produce hyperalgesia. We tested the hypotheses that PGE₂-G is increased in DRGs of HbSS-BERK mice and sensitizes nociceptors (sensory neurons that respond to noxious stimuli), and that blocking its synthesis would decrease hyperalgesia in HbSS-BERK mice. Systemic administration of R-flurbiprofen preferentially reduced production of PGE₂-G over that of PGE₂ in DRGs, decreased mechanical and thermal hyperalgesia, and decreased sensitization of nociceptors in HbSS-BERK mice. The same dose of R-flurbiprofen had no behavioral effect in HbAA-BERK mice (the transgenic control), but local injection of PGE₂-G into the hind paw of HbAA-BERK mice produced sensitization of nociceptors and hyperalgesia. Coadministration of a P2Y6 receptor antagonist blocked the effect of PGE₂-G, indicating that this receptor is a mediator of pain in SCD. The ability of R-flurbiprofen to block the synthesis of PGE₂-G and to normalize levels of 2-AG suggests that R-flurbiprofen may be beneficial to treat pain in SCD, thereby reducing the use of opioids to relieve pain.

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