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**The function of neural Cyclooxygenase-2 in inflammatory pain**

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A cardinal feature of peripheral inflammation is pain. The commonest way of managing inflammatory pain is to utilize drugs which reduce prostanoid production, either non-steroidal anti-inflammatory agents (NSAIDs) or COX-2 selective inhibitors. PGE2 produced after induction of COX-2 in immune cells in inflamed tissue contributes both to the inflammation itself and to pain hypersensitivity, acting on nociceptor peripheral terminals. However, COX-2 is also induced after peripheral inflammation in neurons in the spinal cord, where it generates a central component of inflammatory pain hypersensitivity by increasing neuronal excitation and reducing inhibition. We have made mice with conditional deletion of COX-2 only in neurons and glia to tease out the relative contribution of peripheral and central COX-2 to inflammatory pain hypersensitivity. In these mice, peripheral COX-2 levels and inflammatory response was unaltered, in contrast to severe diminishment of basal expression as well as inducible COX-2 in the spinal cord after peripheral inflammation. Basal nociceptive behaviour and acute chemical hyperalgesia in reaction to formalin was similar in both animal lines, implying no role of constitutively expressed spinal COX-2 for acute nociception. Likewise, after administration of lipopolysacheride (LPS), fever - a process depending on endothelial COX-2 expression- was observed to a similar extend and duration in both lines. Thermal hyperalgesia after paw inflammation with complete Freund' s adjuvant (CFA) developed similarly in both animal strains and could be blocked with a selective COX-2 inhibitor in both the k.o. and the control animal. However, mechanical hypersensitivity after both peripheral soft tissue and periarticular inflammation was abolished in the animals lacking neuronal and glial COX-2. We conclude that COX-2 expression in the central nervous system and not at the site of inflammation is responsible for the development of mechanical hyperalgesia. In contrast, thermal hyperalgesia – which developed normally in central COX-2 deprived animals but could be blocked by a systemic COX-2 inhibitor- seems to rely on COX-2 expression at the site of inflammation. Mechanical pain is a major symptom of many inflammatory conditions, such as postoperative pain and arthritis, and might therefore best be treated by using centrally acting COX-2 inhibitors. Conditions like skin burns, however, where the skin exhibits largely a hypersensitivity against thermal stimuli, might be more suitable for peripherally restricted drug applications. The increasing understanding of the pathophysiological conditions and anatomical locations of various types of pain will hopefully lead to a more targeted and thus more effective approach of pain management.