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The role of matrix metalloproteases in modulating acute morphine-induced analgesia and hyperalgesia

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Opioids especially mu opioid receptor (MOR) agonists remain to be the most effective treatment for cancer pain. MOR is expressed by primary sensoryneurons including small-sized (C-fiber) and medium sized (Aδ-fiber) neurons in the dorsal root ganglia (DRGs). MOR is also expressed in primary afferent terminals and lamina II interneurons in the spinal cord. In addition, opioid produced by immune cells can also elicit peripheral analgesia by activating opioid receptors on nerve terminals. Accumulating evidence from animal and human studies suggests that opioids also produce paradoxical excitatory and hyperalgesic effects. This phenomenon is known as opioid-induced hyperalgesia (OIH), as a result of up-regulation of pronociceptive pathways in the central and peripheral nervous systems. A brief exposure to fentanyl or morphine induces long-lasting hyperalgesia. Matrix metalloproteases (MMPs) consist of a large family of endopeptidases that require Zn^{2+} for their enzyme activity and play a critical role in inflammation through the cleavage of the extracellular matrix proteins, cytokines, and chemokines. The gelatinases MMP-9 and MMP-2 are two of the best-studied MMP family members. MMP-9 is involved in awide range of CNS diseases including Alzheimer's, amyotrophic lateral sclerosis, multiple sclerosis, brainand spinal cord trauma, epilepsy, and stroke. By degrading extracellular matrix, MMP-9 damages the blood-brain barrier, resulting in edema and vascular leakage in the CNS. Recently, we have demonstrated distinct roles of MMP-9 and MMP-2 in neuropathic pain development: (i) Transient MMP-9 up-regulation after nerve injury is critical for the early-phase development of neuropathic pain; (ii) sustained MMP-2 up-regulation maintains neuropathic pain; and (iii) MMP-9 and MMP-2 induce the active cleavage of IL-1b (activation) in early and late-phase of nerve injury, respectively. MMP-9 up-regulation in the spinal cord has also been implicated in chronic opioid-induced withdrawal syndrome (morphine dependence) through possible neuronal activation and interaction with NMDA receptors (NR1 and NR2B) via integrin-beta1 and NO pathways. It is unclear whether MMP-9 also plays a role in acute opioid-induced pronociceptive responses. In this presentation, the author will review the role of MMP in modulating acute morphine-induced analgesia and hyperalgesia in mice.