Opioids produce analgesia via immune cells

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Opioids are the most powerful painkillers. Researchers at the Charité - Universitätsmedizin Berlin have now found that the analgesic effects of opioids are not exclusively mediated by opioid receptors in the brain, but can also be mediated via the activation of receptors in immune cells. These findings represent a novel concept in our understanding of the mechanisms of opioid analgesia. Results from this research, published in the journal *Brain, Behavior, and Immunity*, show that pain reduction in mice was mediated by the activation of opioid receptors in immune cells.

Opioids such as morphine are the gold standard for the treatment of severe pain. Until now, opioids were considered to reduce pain by inhibiting the activity of sensory neurons in the brain. However, most pain conditions are associated with damage to peripheral tissue (skin, joints, viscera), which is infiltrated by immune cells. "This prompted us to ask whether opioids could also inhibit pain by acting on immune cells," explains Prof. Dr. Halina Machelska, a researcher at the Department of Anesthesiology and Critical Care Medicine at the Charité - Campus Benjamin Franklin. "We hypothesized that opioids act at opioid receptors on immune cells and release endogenous opioid peptides such as endorphins, enkepahlins and dynorphins. The secreted opioid peptides would then activate neuronal opioid receptors and reduce pain."

Using an animal model of neuropathic pain and three different exogenous opioids (opioid receptor agonists), the researchers led by Prof. Machelska demonstrated that all three agonists alleviated pain. However, animals with reduced numbers of immune cells experienced

much weaker analgesia. Interestingly, this analgesia was fully restored when the numbers of immune cells were again increased. This effect was only mediated by immune cells containing opioid receptors. "We were able to show that opioid agonists activate opioid receptors on immune cells, which triggered the release of endogenous painkillers (opioid peptides) and produced analgesia in a mouse model of neuropathic pain ," explains Prof. Machelska.

She adds, "This led us to conclude that opioids can exert enhanced analgesia when they act directly in painful tissue - providing that this tissue is inflamed and contain immune cells." These findings are relevant for many pain conditions, including arthritis, nerve damage, post-surgical and cancer pain, since all of them are associated with an immune response. Furthermore, opioids acting directly within peripheral inflamed tissue, outside of the brain, will not produce undesirable effects such as nausea, breathing difficulties, and addiction. These findings provide incentives for the development of new opioids exerting analgesia selectively in peripheral damaged tissue infiltrated by immune cells expressing opioid receptors.

More information: Melih Ö. Celik et al, Leukocyte opioid receptors mediate analgesia via Ca2+-regulated release of opioid peptides, *Brain, Behavior, and Immunity* (2016). DOI: 10.1016/j.bbi.2016.04.018

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