Researchers reveal neural mechanisms underlying opioid analgesia

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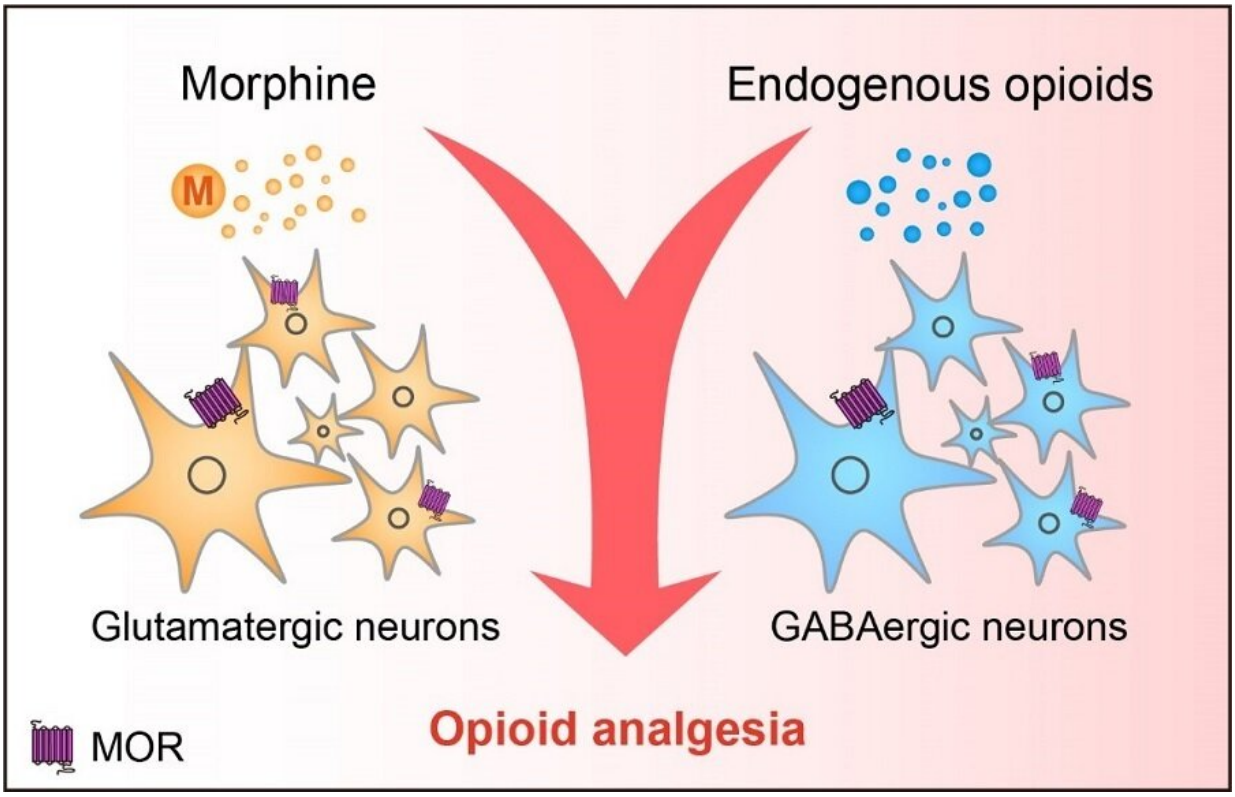

Schematic showing the mechanisms underlying opioid analgesia. Credit: CEBSIT

A new study published in *eLife* by researchers from Dr. Sun Yangang's Lab at the Institute of Neuroscience, Center for Excellence in Brain Science and Intelligence Technology (CEBSIT) of the Chinese Academy

of Sciences has revealed the neural mechanisms underlying opioid analgesia.

Using a combination of genetic, pharmacological and behavioral approaches, the researchers found that analgesic effects of exogenous and endogenous opioids on inflammatory pain are mediated by mu opioid receptors (MORs) expressed in glutamatergic and GABAergic neurons, respectively. This study provides new mechanistic insight into the neural mechanisms underlying pain modulation, paving the way for designing new strategy for pain management.

Pain is a complex experience, and serves as an important protective mechanism, which is critical for the survival of animals and humans. However, chronic pain caused by severe injuries or chronic diseases negatively affects the life quality of patients. Persistent or recurrent pain affects more than 20% of the global population. Therefore, an appropriate and effective analgesic is urgently needed.

Opioids have been used in pain relief for thousands of years, and are still the most powerful analgesics used clinically. However, the long-term use of opioids is limited by numerous adverse side-effects. At present, the neural mechanism of opioid analgesia is not fully understood; thus, further study of opioid analgesia mechanisms could guide clinical opioid drug administration and contribute to the development of novel opioid analgesics with less side effects.

Both exogenous and endogenous opioids exert analgesic effects by acting on MORs, which are widely expressed throughout the nervous system. Using a genetic "knockout first, in situ restoration" strategy, the researchers investigated the functional role of MORs expressed in neuronal populations to elucidate the neural mechanism of opioid analgesia.

They found that exogenous opioids (such as morphine) produce analgesic effect by activating MORs in glutamatergic excitatory neurons, whereas the endogenous opioids relieve chronic inflammatory pain by acting on MORs in GABAergic inhibitory neurons.

Furthermore, the researchers examined the functional role of MORs expressed at peripheral, spinal and supraspinal levels for analgesia.

MORs expressed at the spinal level are mainly involved in the analgesic effect of morphine in acute pain, but not in endogenous opioid analgesia during chronic inflammatory pain. In addition, MORs in the excitatory and inhibitory neurons of the spinal cord play opposite roles in pain modulation. Activation of MORs in excitatory neurons in the spinal cord results in analgesic effects; conversely, activation of MORs in spinal GABAergic neurons induces hyperalgesia. At the supraspinal level, MORs expressed in the parabrachial nucleus are involved in the analgesic effect of morphine on inflammatory pain.

This study, together with the study published online in *Neuroscience Bulletin* in May, 2020 by Dr. Sun's lab, revealed the potential role of MORs in different neuronal populations for opioid analgesia and dependence, providing an important basis for further elucidating the mechanism of opioid action.

More information: Xin-Yan Zhang et al. Different neuronal populations mediate inflammatory pain analgesia by exogenous and endogenous opioids, *eLife* (2020). DOI: 10.7554/eLife.55289

Xin-Yan Zhang et al. Mu-Opioid Receptors Expressed in Glutamatergic Neurons are Essential for Morphine Withdrawal, *Neuroscience Bulletin* (2020). DOI: 10.1007/s12264-020-00515-5