Medical Xpress

Opioid dependence found to permanently change brains of rats

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Approximately one-quarter of patients who are prescribed opioids for chronic pain misuse them, with five to 10 percent developing an opioid use disorder or addiction. In a new study, published Jan. 14, 2020 in

PNAS, researchers at University of California San Diego School of Medicine found that opioid dependence produced permanent changes in the brains of rats.

More specifically, researchers reported that dependence on oxycodone, a potent opioid painkiller, led to permanent neuro-adaptations of the central nucleus of the amygdala (CeA) at the level of the nociceptin system, a brainwide network that modulates transmission of pain. Downregulation or suppression of the nociceptin system in the CeA led to an increase in activation of GABA receptors in rats highly addicted to opioids. The discovery is consistent with previous findings reporting CeA neuroa-daptations after cocaine and alcohol dependence.

When researchers restored nociceptin levels in the CeA, it resulted in normalization of GABAergic transmission and a reduction of the rats' opioid consumption.

"This suggests the nociceptin system may be a promising target for the treatment of opioid use disorder," said senior author Giordano de Guglielmo, PharmD, Ph.D., assistant professor in the Department of Psychiatry at UC San Diego School of Medicine.

"To reveal the role of nociceptin in the central nucleus of the amygdala, we used a multidisciplinary approach with behavioral models, molecular biology and electrophysiology," said first author Marsida Kallupi, PharmD, Ph.D., assistant professor in the Department of Psychiatry. "That allowed us to conclude that downregulation of this peptide may be partially responsible for excessive opioid addiction-like behaviors."

Currently, opioid maintenance therapy is the first-line treatment for opioid dependence, which involves using alternative, less damaging medications, such as methadone, buprenorphine and naltrexone. These three drugs are the only treatments approved by the U.S. Food and Drug

Administration, but all have limitations, either because they act against different receptors, pose safety concerns or are less effective due to the need for strict adherence to treatment.

Both methadone and buprenorphine target mu-opioid receptors in the brain. The new research builds upon past behavioral and neurochemical studies suggesting the nociceptin system and its receptors (NOP) are also involved in opioid tolerance and reward, addiction to multiple drugs and modulation of stress. Interestingly, while the research demonstrates that NOP is implicated in development of opioid dependence, it conversely blocks effects of morphine-based opioids.

De Guglielmo said several efforts are already underway testing small molecule drugs that target the nociception system, and have produced positive effects in reducing alcohol-seeking behaviors and biology in rats. The new findings indicate they may offer similar potential therapeutic benefit for opioid addiction.

Every day, according to the National Institute on Drug Abuse, more than 130 people in the United States die after overdosing on opioids. Two out of three drug overdose deaths involve an opioid. From 1999 to 2017, the last year for which data is available, almost 400,000 Americans lost their lives to opioids, with 47,600 fatal overdoses in 2017 alone. It's estimated 2.1 million Americans have an opioid use disorder.

More information: Marsida Kallupi et al, Nociceptin attenuates the escalation of oxycodone self-administration by normalizing CeA–GABA transmission in highly addicted rats, *Proceedings of the National Academy of Sciences* (2020). DOI: 10.1073/pnas.1915143117

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