MedicalXpress

A new target for alcoholism treatment: Kappa opioid receptors

May 22 2014

The list of brain receptor targets for opiates reads like a fraternity: Mu Delta Kappa. The mu opioid receptor is the primary target for morphine and endogenous opioids like endorphin, whereas the delta opioid receptor shows the highest affinity for endogenous enkephalins. The kappa opioid receptor (KOR) is very interesting, but the least understood of the opiate receptor family.

Until now, the mu opioid receptor received the most attention in alcoholism research. Naltrexone, a drug approved by the U.S. Food and Drug Administration for the treatment of alcoholism, acts by blocking opiate action at brain receptors and is most potent at the mu opioid receptor. In addition, research has suggested that a variant of the gene that codes for the mu opioid receptor (OPRM1) may be associated with the risk for alcoholism and the response to naltrexone treatment.

However, naltrexone also acts at the kappa opioid receptor and it has not been clear whether this effect of naltrexone is relevant to alcoholism treatment.

A growing body of research in animals implicates the KOR in alcoholism. Stimulation of the KOR, which occurs with alcohol intake, is thought to produce unpleasant and aversive effects. This receptor is hypothesized to play a role in alcohol dependence, at least in part, by promoting negative reinforcement processes. In other words, the theory postulates that during development of alcohol dependence, the KOR system becomes overstimulated, producing dysphoria and anhedonia,

which then leads to further alcohol seeking and escalation of alcohol intake that serves to self-medicate those negative symptoms.

A new study in *Biological Psychiatry*, led by Dr. Brendan Walker at Washington State University, used a rat model of alcohol dependence to directly investigate the KOR system following chronic alcohol exposure and withdrawal.

They found that the KOR system is dysregulated in the amygdala of alcohol-dependent rats, a vital brain region with many functions, including regulation of emotional behavior and decision-making. Chronic alcohol consumption is known to cause neuroadaptations in the amygdala. In this study specifically, they found increased dynorphin A and increased KOR signaling in the amygdala of alcohol-dependent rats.

When the rats were in acute alcohol withdrawal, the researchers administered different drugs, each of which target the KOR system in precise ways, directly into the amygdala. Using this site-specific antagonism, they observed that alcohol dependence-related KOR dysregulation directly contributes to the excessive alcohol consumption that occurs during withdrawal.

"These data provide important new support for the hypothesis that kappa opioid receptor blockers might play a role in the treatment of alcoholism," said Dr. John Krystal, Editor of *Biological Psychiatry*. "This study suggests that one role might be to prevent a relapse to alcohol use among patients recently withdrawn from alcohol."

"This dataset demonstrates the extensive nature of the neuroadaptations the brain undergoes when chronically exposed to alcohol. The implications of these results are far reaching and should help guide pharmacotherapeutic development efforts for the treatment of alcohol use disorders," said Walker. "Pharmacological compounds that alleviate

the negative emotional / mood states that accompany alcohol withdrawal, by attenuating the excessive signaling in the dynorphin / kappa-opioid receptor system, should result in enhanced treatment compliance and facilitate the transition away from alcohol dependence."

Additional extensive research will be necessary to identify and test the effectiveness of specific drugs that act on the KOR system, but these findings provide researchers with a potentially successful path forward to developing new drugs for the treatment of alcoholism.

More information: The article is "The One-Two Punch of Alcoholism: Role of Central Amygdala Dynorphins/Kappa-Opioid Receptors" by Jessica L. Kissler, Sunil Sirohi, Daniel J. Reis, Heiko T. Jansen, Raymond M. Quock, Daniel G. Smith, and Brendan M. Walker, DOI: 10.1016/j.biopsych.2013.03.014

Provided by Elsevier