Opioid receptors and mood deficits in protracted abstinence to drugs of abuse

Brigitte L. Kieffer, Douglas Research Center, McGill University, Montréal Canada

Drug abuse is a chronic relapsing disorder with devastating consequences for individuals and their social environment. A major challenge in recovering from addiction is to maintain a drug-free state, also referred to as abstinent state. Prolonged abstinence is characterized by lowered mood and a negative affective state and these emotional dysfunctions are known to contribute to relapse in clinical settings. However, the "abstinence syndrome" has received little attention in preclinical investigations, and the neurobiology of this particular brain state is poorly understood.

We have developed a mouse model of protracted abstinence to chronic morphine, which reflects some aspects of addiction-depression co-morbidity (1). In this model, animals previously exposed to a chronic morphine regimen develop despair-like behavior and social interaction deficits. Behavioral alterations are detectable only after prolonged abstinence. Also, serotonin (5-HT) levels remain altered in the dorsal raphe nucleus (DRN), and Selective Serotonin Uptake Inhibitor (SSRI) treatment during morphine abstinence prevents appearance of the emotional syndrome, indicating a causal implication of the 5-HT system. Finally, behavioral and molecular alterations are also observed upon protracted abstinence to heroin (2) and other drugs of abuse, but not cocaine (3, 4).

We have further shown that endogenous opioid receptor mechanisms are involved in this abstinence syndrome. Data from genetic mouse models by our group and others have positioned all three opioid receptors in the control of hedonic homeostasis and mood (5, 6). We found that mu opioid receptors in the DRN are essential to the development of emotional deficits upon prolonged abstinence to chronic heroin, but do not contribute to withdrawal or cognitive impairments (2). We also found that delta and kappa receptors oppositely influence susceptibility to develop the depressive-like behavior and social withdrawal (2). Also, kappa opioid receptor blockade during or after the abstinence period is able to prevent or reverse the social withdrawal symptom, respectively (7). All three opioid receptors, therefore, contributes to mood deficits associated to drug abstinence.

Future studies will elucidate circuit mechanisms underlying opioid receptor-mediated reward and aversion. In a very recent study (8) we tested whether the sole targeted deletion of one gene –the mu opioid receptor gene- alters whole-brain functional connectivity (FC) in live mice. Hypothesis-free analysis of fMRI data from mutant and control animals showed pronounced modifications of resting-state FC, and captured a unique gene-to-network signature for this gene. Strongest perturbations occurred the reward/aversion circuit, with major influence on negative affect centers. This result opens the way to mechanistic connectome/genetics, and offers promises for translatable investigations of the addicted brain.

(1) Goeldner et al (2011) Biol Psychiatry Feb 1;69(3):236-44.
(2) Lutz et al (2014)Neuropsychopharmacology Oct;39(11):2694-705.
(3) Le Merrer et al (2012) Addiction Biology Jan;17(1):1-12.
(4) Becker et al (2016) Addiction Biology (in press).
(5) Lutz and Kieffer (2013) Neurosci. 2013 36(3):195-206.
(6) Lutz and Kieffer (2013) Curr Opin Neurobiol. 23(4):473-9.
(7) Lalanne et al (2016) Addiction Biology (in press).
(8) Mechling et al (2016) Proceedings of the National Academy of Sciences (in press).