Circuitry involved in opioid reinforcement and aversive states.

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Opioids create a state of well-being and are the standard for treating moderate to severe acute pain, but they also produce potent anxiolytic and antidepressant-like actions. Prolonged opioid taking triggers allostatic processes that are evident following drug cessation, which contributes to withdrawal. Some withdrawal symptoms resolve quickly, such as sweating, chills and other physical symptoms but others may incubate during abstinence including depressive symptoms. Yet other adaptations such as learned associations may be imprinted for life. The drivers of opioid addiction are complex but the comorbidity with mental disorders such as anxiety, depression and PTSD, render individuals susceptible to developing addiction, presumably due to the exacerbation of negative symptoms during withdrawal states and a learned association that such negative symptoms are alleviated by drug use.

Methods: Using genetic mouse models, we are dissecting the circuitry mediating reward-related behaviors, including locomotor effects and different phases of opioid self-administration: acquisition, extinction training and reinstatement. In parallel, we are assessing allostatic processes involved in chronic opioid use and in chronic pain (such as neuroinflammation and modulation of the kappa system) to identify mechanisms mediating negative affect states that drive reward-related behaviors.

Results: The knock-in of mu opioid receptors in striatal D1 (dynorphin-expressing) neurons is sufficient to produce opioid reward as well as locomotor hyperactivity and sensitization. Although, conditional knock-out of mu opioid receptors in D1 expressing neurons (D1-Cre crossed with the Flox-Mu receptor mice) prevents opioid locomotor sensitization, the hyperlocomotor effect of opioids is retained. Mu opioid receptors deleted from all GABAergic forebrain neurons (dlx5/6-Cre crossed with the Flox-Mu receptor mice) have no opioid-induced hyperlocomotor effects. When mu opioid receptors are deleted from either D1 or forebrain GABAergic neurons the acquisition and maintenance of opioid self-administration is unaltered, suggesting that striatal mu opioid receptors are not necessary for reward. During extinction training from oxycodone self-administration, mice show dramatic and enhanced activity on the drug-trained lever. Interestingly, mice with depleted mu receptors in D2 neurons exhibit attenuation of the enhanced activity during extinction. Allostatic changes that likely contribute to dysphoria and drug-seeking include both microglia activation and upregulation of the kappa opioid system following chronic opioid treatments and in chronic pain states.

Discussion: Mu opioid receptors in D1 or D2 receptor containing neurons play a significant role in opioid reward-related behaviors and convincingly dissociate drug self-administration from drug-induced hyperlocomotor effects. Future research will address the role of pain, neuroinflammation and the kappa system in the different phases of opioid self-administration.

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