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Probing Neuronal Circuit Dynamics: Calcium Imaging Comparison of a Novel Mu Opioid Agonist and Oxycodone Effects in the Medial Prefrontal Cortex

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Opioid use disorder (OUD) remains a significant public health issue, yet the neurocircuitry underlying opioid addiction and withdrawal is poorly understood. This study uses in vivo single-photon calcium imaging in awake, behaving mice to examine the effects of opioids on neural activity in the medial prefrontal cortex (PFC), a region critical for reward processing and pain signaling.

We utilized genetically encoded calcium indicators to record activity in glutamatergic and GABAergic neurons in the PFC of male and female B6129 mice, both during oxycodone and the novel mu-opioid receptor agonist, atoxifent, administration, as well as during protracted withdrawal. Simultaneously, antinociceptive responses were assessed using the hot plate assay. Atoxifent, a synthetic opioid with potent analgesic properties, demonstrated similar effects to fentanyl but with reduced respiratory depression, suggesting potential advantages for therapeutic use.

Our findings reveal distinct activity patterns between excitatory and inhibitory neurons in the PFC during opioid administration and withdrawal. Specifically, certain neural populations remain inactive during baseline and drug exposure but become active during withdrawal, potentially contributing to the negative effects of opioid cessation. Corresponding changes in antinociceptive responses support these observations. These results provide new insights into the neurocircuitry of opioid withdrawal and offer potential targets for therapeutic intervention in OUD treatment.
This work highlights the importance of region-specific, real-time neural activity monitoring in understanding the long-term effects of opioids on brain function, with implications for drug addiction research and treatment strategies.