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A master regulator of opioid reward in ventral prefrontal cortex

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In addition to their rewarding properties, opioids can also evoke aversive reactions that protect against misuse. Cellular mechanisms that govern the interplay between reward and aversion are not well understood. We used whole-brain activity (c-Fos) mapping in C57BL6/J mice to show that neurons in the dorsal peduncular nucleus (DPn) of the ventral prefrontal cortex are highly responsive to the opioid oxycodone. Spatial and single-nuclei sequencing of the DPn identified a population of deep-layer pyramidal neurons that co-express *Oprm1* and *Slc17a6* (vGluT2), a highly unique cell population within the cortex. Connectomic profiling revealed that DPn neurons project to the parabrachial nucleus (PBn). Using C57, FosTRAP2, and vGluT2-Cre mice, we found that optogenetic stimulation of opioid-responsive neurons in the DPn or their terminals in the PBn induce avoidance behavior in opioid-naïve mice, and augments symptoms of naloxone-precipitated withdrawal in opioid-dependent mice. Furthermore, selectively knocking down *μ* receptor expression in the DPC via AAV-Cre injection into *Oprm1*$^{flox/flox}$ mice reversed the hedonic valence of oxycodone, such that these mice formed a conditioned place aversion in response to a 5mg/kg oxycodone dose that induced a conditioned place preference in AAV-mCherry injected control mice. Together these data indicate that the DPC is a novel opioid-responsive component of the vmPFC, and that *Oprm1/vGluT2* expressing neurons in this region regulate the rewarding and aversive properties of opioid exposure and withdrawal.