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Identification and manipulation of dopamine neurons recruited by fentanyl self-administration

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The opioid epidemic in this nation has continued to surge amidst 1 in 3 adults suffering from a chronic pain disorder. The search for a less addictive but optimally effective treatment to replace opioids remains at the forefront of national goals. Dopamine (DA), especially from the ventral tegmental area (VTA) to the nucleus accumbens (NAc) has been implicated in addiction of all types, including to opioids. Due to the myriad functions of DA, an ability to target a distinct group may provide cleaner results than pan-dopaminergic investigation. DA subpopulations are molecularly and genetically defined, and allow uniquely specific targeting of its circuitry. First, we designed an unbiased genetic screen, using a tamoxifen-inducible cFos in a DA-neuron-specific transgenic mouse line, that allowed us to capture DA neurons active in the presence of self-admiration of fentanyl. Based on this capture, we found a bias towards one subpopulation (marked by Aldh1a1 expression) which also projects from the VTA to NAc. Using Aldh1a1 and DA transgenic mice and intersectional genetic viral techniques, we examined the impact of silencing just that subpopulation over others or all DA. We then provide the molecular signature which would allow specific targeting of just the DA involved in opioid addiction, while leaving analgesic functions intact. By defining opioid-recruited DA subpopulations, we can now determine the importance of these populations in addiction-related behaviors. These studies could open a novel group of molecular pharmacologic targets to prevent opioid addiction.