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ADDICTION

Road to aversion

Long-term use of opiates can lead to dependence, whereby cessation of drug-taking induces negative emotional and physical symptoms. Avoidance of these withdrawal symptoms is a reinforcing factor underlying continuing opiate use; however, little is known about the circuitry underlying withdrawal. Zhu *et al.* now show that a pathway from the paraventricular nucleus of the thalamus (PVT) to the nucleus accumbens (NAc) mediates the behavioural response to opiate withdrawal in mice.

The authors identified a direct projection to the NAc from the PVT, a region that had previously been implicated in opiate-seeking behaviour. To determine the role of the PVT–NAc pathway in normal behaviour, the authors placed mice in a two-chamber conditioned place preference (CPP) apparatus. Entry to one of the chambers triggered optogenetic stimulation of PVT terminals in the NAc that continued until they exited the chamber. This stimulation resulted in behavioural avoidance to the stimulation-paired chamber.

Next, the authors investigated the role of the PVT–NAc pathway in opiate withdrawal. Mice received six daily escalating doses of morphine,

after which withdrawal was induced by administering the μ -opioid receptor antagonist naloxone. This regime normally induces immediate physical signs of withdrawal (including tremors, jumping and rearing), and conditioned place aversion (CPA) to the site where the naloxone injection took place. All of these effects were reduced in mice in which PVT terminals in the NAc had been optogenetically silenced after naloxone administration.

The authors also investigated the role of the PVT–NAc pathway in spontaneous opiate withdrawal. Mice were given daily morphine injections over 4 days, and 16 hours after each injection (when the mice express withdrawal) they were confined to one side of the CPP apparatus. Testing of these mice after the final day of morphine injection showed that mice in which the PVT–NAc pathway had been pharmacogenetically inactivated during CPP training showed less avoidance to the chamber that they were confined to during training than control mice that had not undergone pharmacogenetic manipulation. Thus, the PVT–NAc pathway also contributes to the aversive effects of spontaneous opiate withdrawal.

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Using targeted whole-cell recording in mouse brain slices, the authors showed that five escalating daily doses of morphine induces synaptic strengthening in the NAc — specifically, between PVT neurons and dopamine D2 receptor-expressing medium spiny neurons of the NAc (D2 MSNs) — as a result of increased insertion of calcium-permeable AMPARs to the postsynaptic membrane. Furthermore, in mice that had received six daily escalating doses of morphine before naloxone-induced withdrawal, an optogenetically induced long-term depression protocol was used to show that depotentiation of PVT–D2 MSN synapses reduced the expression of physical withdrawal symptoms and the development of CPA.

Together, these findings reveal that the previously uncharacterized pathway from the PVT to the NAc contributes to signs of opiate withdrawal. Reversing the plasticity of PVT–D2 MSN synapses in the NAc may be a promising therapeutic strategy for individuals who are dependent on opiates.

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ORIGINAL ARTICLE Zhu Y *et al.* A thalamic input to the nucleus accumbens mediates opiate dependence. *Nature* **530**, 219–222 (2016)