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ADDICTION

Craving: a core issue

> spine head diameter and A/N ratio correlated with the number of reinstated active lever presses

A major problem in overcoming drug addiction is the craving that is induced by cues and contexts associated with drug taking, as this can lead to relapse. Kalivas and colleagues now show that cue-induced relapse of cocaine taking in rats is associated with fast and transient synaptic potentiation in the nucleus accumbens (NAc) core.

Rats were trained to self-administer cocaine in a design in which pressing one of two levers (the active lever) triggered an intravenous infusion of the drug and, simultaneously, a light and a tone; pressing the other (inactive) lever had no consequence. After 10 days of training, rats underwent an extinction procedure, in which an 'active' lever press no longer had any effect. Lever pressing decreased accordingly, until a baseline number of presses remained. At this time point (T0), pressing the previously active lever was again paired with the light and tone cue. This triggered a marked reinstatement of lever pressing, presumably reflecting the rat's attempts to get cocaine — a model of cue-induced relapse. The increase in lever pressing was greatest in the first 10 minutes of reinstatement, after which it gradually decreased.

The authors showed in NAc tissue slices from these rats that after cocaine training and extinction (that is, before reinstatement), medium spiny neurons (MSNs) in the NAc core had larger spine head diameters and a higher ratio of AMPA currents to NMDA currents (A/N ratio) compared with control rats, indicating synaptic potentiation. Cue-induced reinstatement further increased the spine head diameter and A/N ratio at T15, but both measures had returned to pre-reinstatement levels by T120. Interestingly, at T15, the spine head diameter and A/N ratio correlated with the number of reinstated active lever presses.

The reinstatement-induced synaptic potentiation was specific for cocaine: when the authors repeated the experiment using the natural reward sucrose, the rats showed cue-induced behavioural reinstatement without any changes in spine head diameter or A/N ratio.

Finally, the authors showed that inhibiting activity in the prelimbic cortex before reinstatement, by microinjecting GABA agonists, prevented the cue-induced reinstatement of lever pressing and synaptic potentiation in NAc MSNs. This suggests that inputs from the prelimbic cortex into the NAc are crucial for cue-induced reinstatement of cocaine seeking.

The finding that cues associated with cocaine, but not cues associated with sucrose, can induce rapid, transient changes in the NAc may explain why cue-induced drug cravings are harder to resist than cue-induced cravings for natural rewards. Also, synaptic plasticity that appears to be unique to drug craving and relapse suggests the possibility of targeting drug addiction without affecting other motivated behaviours.

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PhotoDisc

ORIGINAL RESEARCH PAPER Gipson, C. D. *et al.* Relapse induced by cues predicting cocaine depends on rapid, transient synaptic potentiation. *Neuron* **77**, 867–872 (2013)
FURTHER READING Kalivas, P. W. The glutamate hypothesis of addiction. *Nature Rev. Neurosci.* **10**, 561–572 (2009)