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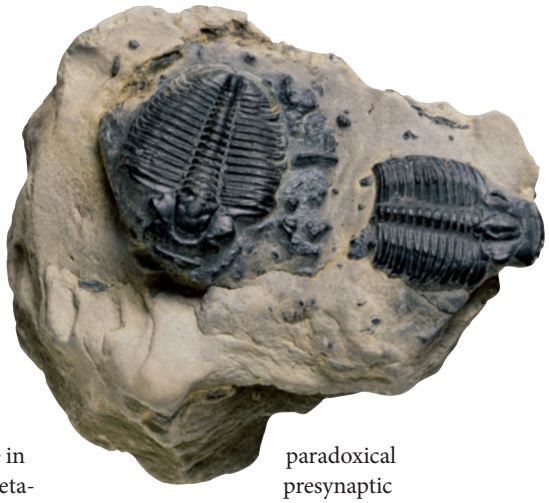
ADDICTION

Lasting impressions



Relapse is one of the major problems that people face when trying to overcome drug addiction, but the changes that occur in the dorsal striatum — an area that is thought to be involved in habit formation — during drug exposure and withdrawal and that might cause craving and relapse are unclear. However, a new study by Bamford *et al*. reveals that withdrawal from chronic methamphetamine exposure induces long-lasting changes in cholinergic and dopaminergic receptors at corticostriatal synapses and altered synaptic functioning that is restored by re-administration of the drug.

The authors investigated corticostriatal signalling in mice using electrochemistry, electrophysiology and an optical imaging technique in which a fluorescent dye was used to quantify the release of the neurotransmitter glutamate from individual corticostriatal terminals in slice preparations. The tracer was taken up by presynaptic vesicles and released upon stimulation of the cortical neurons.

A single dose of methamphetamine reduced corticostriatal release, but repeated (10-day) administration of the drug followed by a period of withdrawal resulted in a much stronger, long-lasting reduction of release. This phenomenon, which the authors termed chronic presynaptic depression (CPD), was evident after 10 days of drug withdrawal and lasted at least 140 days.

Methamphetamine is known to increase synaptic dopamine release, suggesting that long-lasting changes in dopamine signalling induced by repeated methamphetamine exposure might underlie CPD. However, the authors found no changes in electrically evoked or amphetamine-induced dopamine release in mice after 10 days of methamphetamine withdrawal, suggesting that dopamine is required to initiate these long-lasting synaptic changes but is not necessary for their maintenance.

Repeated methamphetamine administration did reduce striatal acetylcholine (ACh) levels during withdrawal. Furthermore, blocking nicotinic ACh receptors (nAChRs) — which mediate ongoing, tonic ACh signalling — inhibited corticostriatal release in slices from naive mice but had no effect in slices from methamphetamine-withdrawal mice, indicating a loss of tonic ACh excitation during methamphetamine withdrawal. In addition, a lower concentration of a muscarinic ACh receptor (mAChR) agonist was required to inhibit corticostriatal release in withdrawal animals than in control animals, which was suggestive of increased mAChR sensitivity. Thus, repeated methamphetamine treatment followed by withdrawal resulted in CPD, owing to both decreased tonic stimulation of corticostriatal release through nAChRs and increased tonic inhibition of release through sensitized mAChRs on corticostriatal terminals.

The authors also showed that the CPD could be reversed by a single re-administration of methamphetamine or amphetamine on day 10 of withdrawal; this was referred to as paradoxical presynaptic potentiation (PPP). Dopamine D1 receptor (D1R) ligands had no effect in saline-treated mice, but treating slices from withdrawal mice with a D1R agonist also caused PPP, whereas a D1R antagonist reversed amphetamine-induced PPP. In addition, the CPD that was observed in slices from withdrawal mice was normalized by a low dose of nicotine or ACh, and this effect was inhibited by a nAChR antagonist. Thus, both D1R activation by methamphetamine-induced dopamine release and nAChR stimulation contributed to PPP.

This study has shown that chronic methamphetamine administration induces long-lasting synaptic changes through an adaptation of striatal D1Rs and AChRs, and that re-administration of the drug reverses these alterations in synaptic functioning. Whether or how these findings relate to other alterations in synaptic plasticity that have been reported in addiction requires further investigation, but nevertheless they might provide potential treatment targets.

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ORIGINAL RESEARCH PAPER Bamford, N. S. *et al*. Repeated exposure to methamphetamine causes long-lasting presynaptic corticostriatal depression that is renormalized with drug readministration. *Neuron* **58**, 89–103 (2008)