ADDICTION

Targeting neural correlates of addiction

Repeated exposure to drugs of abuse such as amphetamine, cocaine and nicotine can lead to long-lasting changes in the strength of synaptic transmission in mesocorticolimbic regions of the brain. Using new synthetic peptide inhibitors of a specific type of synaptic plasticity — the long-term depression (LTD) of excitatory neurotransmission — Brebner, Wong and colleagues identify molecular components of a neural adaptation that might underlie drug craving in addicts.

The drug-induced behavioural sensitization of motor activity — in which a long-lasting increase in the locomotor stimulatory effects of a drug of abuse is seen after repeated administration — is used to model some of the core features of addiction and the development of drug-induced psychosis. Changes in synaptic strength in the ventral tegmental area (VTA) are associated with the induction of behavioural sensitization, whereas synaptic plasticity in the nucleus accumbens (NAc), which receives dopaminergic projections from the VTA, seems to be responsible for its long-term expression.

In particular, enhanced LTD of glutamatergic transmission in the NAc has been identified as a neural correlate of behavioural sensitization to cocaine. Now Brebner *et al.* take an important step further by providing insights into the molecular mechanisms that underlie NAc LTD and the expression of behavioural sensitization to amphetamine.

To find out whether facilitated endocytosis of postsynaptic AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid) receptors contributes to LTD in the NAc, as it does in the hippocampus, the researchers recorded excitatory postsynaptic currents evoked by the stimulation of cortical glutamatergic inputs to medium spiny neurons in the shell region of the NAc. A dynamin-derived synthetic peptide that inhibits clathrin-mediated endocytosis (by blocking the recruitment of dynamin to clathrin-coated pits) prevented the expression of LTD, as did a synthetic peptide derived from the AMPA receptor subunit GluR2, which specifically blocked the regulated endocytosis of AMPA-type glutamate receptors.

The researchers then used a membrane-permeant form of GluR2 peptide to target NAc LTD in freely moving rats. The peptide blocked the expression of amphetamine-induced behavioural sensitization, raising the interesting question of whether GluR2-dependent AMPA receptor endocytosis is involved in the intensification of drug craving seen in human addicts with repeated drug exposure.

This study highlights the value of peptides that specifically disrupt the final step in the expression of synaptic plasticity in studying the neural correlates of behavioural sensitization. The researchers propose that such peptides could also provide a basis for the development of drugs to treat the maladaptive neural adaptations associated with drug addiction.

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ORIGINAL RESEARCH PAPER Brebner, K. *et al.* Nucleus accumbens long-term depression and the expression of behavioral sensitization. *Science* **310**, 1340–1343 (2005)
FURTHER READING Thomas, M. J. *et al.* Long-term depression in the nucleus accumbens: a neural correlate of behavioral sensitization to cocaine. *Nature Neurosci.* **4**, 1217–1223 (2001) | Hyman, S. E. & Malenka, R. C. Addiction and the brain: the neurobiology of compulsion and its persistence. *Nature Rev. Neurosci.* **2**, 695–703 (2001)