DRUG ADDICTION

Blocking cocaine-seeking behaviour

An effective treatment for cocaine addiction is lacking. A recent paper in *Nature Medicine* has shown how an inhibitor of the enzyme aldehyde dehydrogenase 2 (ALDH2) suppresses addictive behaviour in response to cocaine administration, suggesting its potential in the treatment of addiction and the prevention of relapse behaviour.

Dopaminergic neurotransmission between the ventral tegmental area (VTA) and the nucleus accumbens has a major role in addictive behaviours, and so reducing dopamine levels in these brain regions could have therapeutic value. In this study, the authors investigated whether a selective ALDH2 inhibitor — which is known to reduce alcohol-seeking behaviour — can suppress cocaine-seeking behaviour by reducing drug-associated increases in dopamine synthesis.

In a neuron-derived cell line, cocaine administration increased extracellular and intracellular dopamine levels, which were prevented by the selective ALDH2 inhibitor CVT-10216. In rats, intraperitoneal injection of CVT-10216 reduced cocaine self-administration and prevented cocaine-induced or cue-induced cocaine relapse-like behaviour.

The authors next investigated the mechanism by which ALDH2 inhibition reduces cocaine-seeking behaviour. ALDH2 — which is highly expressed in dopaminergic neurons — converts 3,4-dihydroxyphenylacetaldehyde (DOPAL; generated from dopamine by monoamine oxidase) to 3,4-dihydroxyphenyl-acetic acid. When ALDH2 is inhibited, concentrations of DOPAL increase, which allows DOPAL to condense with dopamine and to form tetrahydropapaveroline (THP). So the authors searched for evidence that selective inhibition of ALDH2 induces the formation of THP during cocaine-activated dopamine production. Indeed, in cocaine-treated neuronal cells, CVT-10216 increased THP formation. This increase in THP inhibited dopamine production through negative-feedback inhibition of tyrosine hydroxylase — the rate-limiting enzyme in dopamine synthesis.

Further work showed that THP inhibited the phosphorylated (activated) form of tyrosine hydroxylase much more effectively than the unphosphorylated enzyme. Phosphorylation occurs when cocaine increases extracellular dopamine, which activates dopamine D2 receptors, stimulating protein kinase A and protein kinase C signalling. So, cocaine administration leads to the activation of tyrosine hydroxylase by phosphorylation. Under these conditions CVT-10216 increases THP levels, which reduces tyrosine hydroxylase activity and therefore dopamine production.

Finally, the authors validated the role of THP in the mechanism of action of CVT-10216 by showing that in models of cocaine relapse-behaviour associated with increased dopamine levels, rats pretreated with the inhibitor had increased THP levels in the VTA and decreases in dopamine levels in the VTA and nucleus accumbens, which correlated with decreases in tyrosine hydroxylase phosphorylation and the suppression of cocaine-seeking behaviour. Importantly, CVT-10216 only affected cocaine-induced increases in dopamine synthesis; there was no effect on basal dopamine levels.

Although, as noted by the authors, additional cocaine-seeking models should be used to extend these results, this study highlights a new mechanism by which ALDH2 inhibition modulates dopamine production in the brain and suggests that ALDH2 inhibitors have the potential to suppress cocaine administration and to prevent relapse in humans.

Charlotte Harrison

ORIGINAL RESEARCH PAPER Yao, L. *et al.* Inhibition of aldehyde dehydrogenase-2 suppresses cocaine seeking by generating THP, a cocaine use-dependent inhibitor of dopamine synthesis. *Nature Med.* **16**, 1024–1028 (2010)