Cannabinoid activity curtails cocaine craving

Behavioral studies demonstrate that the central mechanism involved in cocaine relapse is closely linked to the sites where marijuana has its effect, suggesting that cannabinoid receptor antagonists may be used as anti-craving agents. (pages 1151–1154)

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Although the use of psychoactive drugs begins as a voluntary behavior, in addicted individuals it becomes as uncontrollable as the compulsive, ritualized acts that afflict obsessive-compulsive disorder patients. The overpowering nature of drug addiction and the associated changes in brain structure and function have led to conceptualization of this condition as a chronic disease of the central nervous system. Like other chronic brain diseases, drug addiction goes through recurrent cycles of remission and relapse, which can be readily triggered when abstinent addicts are confronted with reminders of their drug habit ('conditioned cues') or with emotional distress. The prevention of such relapses is thus one of the primary goals of addiction treatment[1].

Relapse to drug taking can be modeled in laboratory animals. In one such model, the 'reinstatement paradigm', cocaine self-administration is first induced in rats and then extinguished by subjecting the animals to a period of abstinence. After drug taking has stopped, exposure to stress, administration of low doses of cocaine or presentation of cocaine-associated cues will cause the behavior to reappear. Regardless of the stimulus, relapses are accompanied by increased activity of the mesolimbic dopamine system—a neural pathway comprising a small group of dopamine-releasing cells in the midbrain connected to a much larger field of dopamine-responsive neurons in the forebrain's nucleus accumbens and prefrontal cortex (Fig. 1). This pathway is thought to be activated in behaviors such as eating and mating, and to underlie the rewarding properties of many psychoactive drugs, but its exact role in drug craving and relapse is only partially understood. One key question is what neurotransmitter systems interact with this mesolimbic dopamine pathway during relapse. In this issue, a study by De Vries *et al*. may provide an answer[2]. In doing so, the study opens up an unexpected avenue for the preventive therapy of cocaine relapse[2].

De Vries *et al*. used the rat reinstatement model to test whether cannabinoid receptors—the target of the marijuana constituent Δ9-tetrahydrocannabinol—have a role in cocaine relapse. They show that the cannabinoid agonist HU-210 precipitates relapse, whereas the cannabinoid antagonist SR141716A prevents relapse induced by cocaine or cocaine-associated cues, but not relapse induced by stress. Because SR141716A has no effect on cocaine self-administration[3], these findings suggest that cannabinoid receptors may be selectively involved in triggering cocaine craving during abstinence, rather than in mediating the primary effects of the drug. That cannabinoid receptors should be implicated in reward is intuitive—millions of marijuana users can testify to that—but that these receptors should also gate cocaine relapse is more surprising. How might it occur?

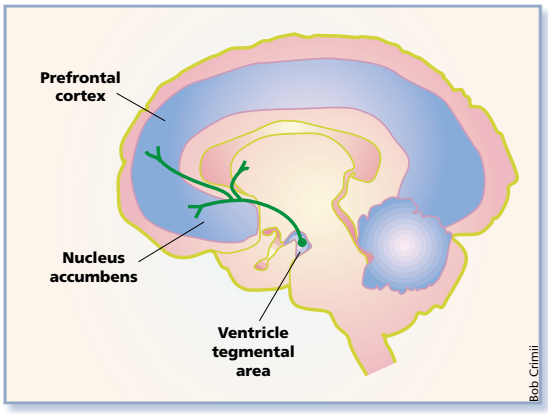

Fig. 1 Cocaine craving is thought to be associated with activation of the mesolimbic dopamine system. This neuromodulatory pathway projects from the ventral tegmental area (VTA) in the midbrain to the nucleus accumbens and the prefrontal cortex. Stress and drug-associated cues may activate the mesolimbic dopamine system by engaging two distinct brain regions, the prefrontal cortex and the amygdala, respectively, that send excitatory projections to the VTA. Presynaptic cannabinoid receptors are present in these brain areas, where their primary role may be to modulate γ-aminobutyric acid (GABA) and glutamate release.

Cannabinoid receptors present in the brain belong largely to the CB1 subtype, although evidence for the existence of other subtypes is accumulating[4]. CB1 receptors are coupled to $G_{i/o}$ proteins and are normally activated by a small group of endogenous lipids called endocannabinoids, of which anandamide and 2-arachidonylglycerol are two well-studied examples. Unlike neurotransmitters and neuropeptides, endo-cannabinoids are not stored in synaptic vesicles but are produced on demand and released from neurons[5]. Two neurotransmitter systems have been linked to the generation of endocannabinoids: dopamine elicits anandamide release in the dorsal striatum by stimulating D_2-type receptors[6], while glutamate causes 2-arachidonylglycerol formation in the cortex by engaging NMDA (*N*-methyl-D-aspartate) receptors[6,7].

To explain their results, De Vries *et al*. outline two possible scenarios that are based on a dopamine–endocannabinoid connection. In one model, elevated dopamine levels produced by cocaine or cocaine-associated cues elicit the release of endocannabinoids, which cause relapse. Alternatively, cocaine or cocaine-associated cues elevate endocannabinoid levels, which cause relapse by enhancing dopamine release. Because the brain's cannabinergic pathways are still uncharted, we lack hard evidence to support either scenario. Yet, the latter hypothesis—that of a disinhibitory role for the endocannabinoids on dopamine transmission—is supported by three observations: CB1 receptors are found in high numbers on axon terminals of γ-aminobutyric acid (GABA)-ergic interneurons throughout the central nervous system; activation of these receptors inhibits GABA release[8]; and GABA-ergic interneurons strongly influence the activity of dopaminergic projection neurons.

Irrespective of the cellular mechanism, the finding that blockade of cannabinoid receptors prevents cue-mediated relapses to cocaine seeking is of obvious therapeutic significance. There is no pharma-

cological treatment for cocaine relapse at present, and even though there are many social and psychological factors that can facilitate relapse, an agent that 'takes the edge off' craving would provide an invaluable complement to behavioral therapy and psychotherapy. Moreover, as commonality emerges in the mechanism by which these drugs are addictive, the therapeutic range of cannabinoid antagonists may be expanded to include other abused substances, such as opiates and alcohol. Animal studies suggest that cannabinoid receptor blockade may alleviate both heroin and alcohol craving[2,9,10]. One possible reservation to the use of cannabinoid antagonists in relapse therapy is that these molecules may not be able to prevent stress-induced relapse, as shown by De Vries *et al*. However, other agents such as non-peptide antagonists of corticotropin-releasing factor receptors may adequately control this condition[11]. As with other chronic diseases, it is reasonable to expect that treatment of drug craving and relapse will involve the use of more than one drug.

1. O'Brien, C.P. A range of research based pharmacotherapies for addiction. *Science* **278**, 66–70 (1997).
2. De Vries, T.C. *et al*. A cannabinoid mechanism in relapse to cocaine seeking. *Nature Med*. **7**, 1151–1154 (2001).
3. Fattore, L., Martellotta, M.C., Cossu, G., Mascia, M.S. & Fratta, W. CB1 cannabinoid receptor agonist WIN 55,212-2 decreases intravenous cocaine self-administration in rats. *Behav. Brain Res*. **104**, 141–146 (1999).
4. Hajos, N., Ledent, C. & Freund, T.F. Novel cannabinoid-sensitive receptor mediates inhibition of glutamatergic synaptic transmission in the hippocampus. *Neuroscience* (in press).
5. Piomelli, D., Giuffrida, A., Rodríguez de Fonseca, F. & Calignano, A. The endocannabinoid system as a target for therapeutic drugs. *Trends Pharmacol. Sci*. **21**, 218–224 (2000).
6. Giuffrida, A. *et al*. Dopamine activation of endogenous cannabinoid signaling in dorsal striatum. *Nature Neurosci*. **2**, 358–363 (1999).
7. Stella, N. & Piomelli, D. Receptor-dependent formation of endogenous cannabinoids in cortical neurons. *Eur. J. Pharmacol*. **425**, 189–196 (2001).
8. Kátona, I. *et al*. Presynaptically located CB1 cannabinoid receptors regulate GABA release from axon terminals of specific hippocampal interneurons. *J. Neurosci*. **19**, 4544–4558 (1999).
9. Gallate, J.E. & McGregor, I.S. The motivation for beer in rats: effects of ritanserin, naloxone and SR141716. *Psychopharmacology* **142**, 302–308 (1997).
10. Colombo, G. *et al*. Reduction of voluntary ethanol intake in ethanol-preferring SP rats by the cannabinoid antagonist SR-141716. *Alcohol Alcohol*. **33**, 126–130 (1998).
11. Shaham, Y., Erb, S. & Stewart, J. Stress-induced relapse to heroin and cocaine seeking in rats: A review. *Brain Res. Rev*. **33**, 13–33 (2000).

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The alternative to penicillins

Methicillin-resistant *Staphylococcus aureus* infections have become a major problem worldwide. The finding that two bacterial enzymes, one native and one acquired, cooperate to build cell walls in the presence of methicillin has drawn attention to an as yet unutilized target for new antibiotics.

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The widespread use of antibiotics led to the cure of infections but also to the rise of resistant—even multiply resistant—bacterial strains. The continuing and increasing threat of drug-resistant bacterial pathogens, particularly ones that emerge in hospitals, must be met by developing new antibiotics. In a recent publication[1], Tomasz and colleagues demonstrate the importance of a crucial enzymatic reaction involved in cell-wall metabolism to methicillin resistance in *Staphylococcus aureus*. The report supports the view that one of the most promising biochemical pathways in which to identify new antibiotic targets is the metabolism of the bacterial exoskeleton, or the peptidoglycan (murein) layer—the target of the β-lactams, which are the most important current antibiotics. There are two main reasons for this: peptidoglycan is found only in bacteria, and the pathway is extracellular, therefore easily available to drugs.

The bacterial cell wall has to withstand an intracellular osmotic pressure of several atmospheres and is reinforced by a kind of exoskeleton made of peptidoglycan (murein). The chemical design of murein—a cross-linked polymer in which sugar strands are interlinked by peptide bridges—makes it ideally suited to act as a cell-wall scaffold[2]. Moreover, the murein netting forms a covalently closed hollow body that completely envelopes the bacterium, much like a string bag. Just as the strength and tightness of a string bag depend on every single mesh in the netting, so do those of the bag-shaped murein sacculus. The murein sacculus is formed by the polymerization of a peptidyl-disaccharide precursor in two directions: peptidyl moieties are hooked to one another by transpeptidation reactions and disaccharides are polymerized to long glycan chains by transglycosylation reactions (Fig. 1)[3–5]. The mechanical strength of the murein fabric critically depends on perfect coordination of the two different polymerization reactions. Interfering with either transglycosylation or transpeptidation results in a fragile murein sacculus that can eventually rupture. Interestingly, nature designed bifunctional enzymes consisting of a transglycosylase and a transpeptidase domain[6,7]. With such enzymes, the two polymerizing reactions are automatically coordinated, thereby minimizing the chance of imperfections in the murein polymer.

Penicillin and the entire β-lactam family of compounds are among the most efficient antibiotics; they act by inhibiting the transpeptidation reactions that lead to cross-linking of the murein strands. Penicillin is structurally similar to the D-alanyl-D-alanyl moiety of the murein precursor that is recognized by the transpeptidases. Thus, in the presence of penicillin, a stable penicilloyl–enzyme complex is formed that irreversibly blocks the enzyme[6,7] Most bacteria are equipped with several transpeptidases, both bifunctional and monofunctional, that are specifically involved in different growth processes, such as cell enlargement and cell division[8]. Because penicillin binds covalently to the transpeptidation site of these enzymes, they are known collectively as penicillin-binding proteins (PBPs). Along with the murein-synthesizing D.D-transpeptidases, this family includes the murein modifying D.D-endopeptidases and the D.D-carboxypeptidases[6,7].

Bacterial resistance to β-lactams evolved mainly through three mechanisms[9]: (i) synthesis of β-lactamases that degrade penicillin; (ii) in Gram-negative bacteria, decreases in the permeability of the outer membrane,