'Unlearning' addiction

Addiction to drugs like cocaine, nicotine and alcohol is often a chronic, relapsing disorder with serious consequences for the drug user and for society as a whole. Addiction can be very difficult to overcome, in part because addictive drugs rewire neural circuits involved in the brain's reward system. This can help form powerful memories of cues associated with drug use that include people, places, sights and sounds. Cue memory drives continued drug use as well as relapse when an addict is exposed to drug-associated cues. Scientists now report a way to erase cue memory in rats by pharmacologically interfering with the rewiring of the brain circuit that underlies its formation.

The treatment was developed by neuroscientists at The University of Texas at Austin led by Hitoshi Morikawa. They trained male Sprague Dawley rats to associate a compartment of a specific color (either black or white) with administration of cocaine or ethanol; once trained, the rats almost always chose to enter the compartment associated with the drug, when given a choice between two compartments.

The researchers then infused the brains of the trained rats with a compound called isradipine before the rats made their choices. Isradipine is used to treat hypertension and is also being investigated for its potential to slow neurodegeneration in Parkinson's disease. When tested on the same day when they received the isradipine infusion, rats still chose the compartment associated with the drug, but when tested on the next two days, they no longer showed a preference for that compartment (*Mol. Psychiatry* doi:10.1038/mp.2015.84; published online 23 June 2015). Even after two weeks of drug withdrawal, when the rats were exposed to the drug again and then given a choice between two compartments, those that received isradipine showed no preference for the compartment associated with the drug. "The isradipine erased memories that led them to associate a certain room with cocaine or alcohol," said Morikawa in a press release.

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Antihypertensive drugs like isradipine block a type of ion channel found in various cells including certain brain cells. Blocking these channels in the brain seemed to reverse the rewiring that underlies cue memory in rats, causing them to 'unlearn' the association between the drug and the compartment in which it was administered. "This drug might help the addicted brain become de-addicted," Morikawa explained, although it remains to be seen whether the strategy will prove effective at counteracting addiction in humans.

Monica Harrington

VARIATION AIDS VIRULENT INVADERS

Haemophilus influenzae encompasses several strains of bacteria that are opportunistically pathogenic in humans, mostly in infants and young children. Nontypable *Haemophilus influenzae* (NTHi) is a predominant cause of infections in the middle ear, or otitis media, which often require treatment with antibiotics or the insertion of ear tubes. Like many bacterial pathogens, NTHi exhibits phase variation, a mechanism whereby different parts of the same bacterial population can express the same gene differentially. In some cases, phase variation can modulate genes that contribute to virulence, causing disease with one phenotype and causing no symptoms with another.

Recent work by Michael P. Jennings of Griffith University (Gold Coast, Australia) and colleagues has examined this characteristic in NTHi, analyzing pathogenic strains to understand how phase variation of a gene for DNA methyltransferase, termed *modA*, effects phenotypes that contribute to bacterial virulence (*Nat. Commun.* **6**, 7828; 2015). Jennings' team created natural 'ON' and 'OFF' strains of NTHi, in which different alleles of *modA* were fully expressed or disrupted throughout populations of NTHi. They then put these strains through a series of tests to determine whether certain traits might be common or differentially expressed during phase variation. These tests showed that phase variation of *modA* alleles influences factors such as antibiotic susceptibility and immunoevasion.

Finally, the researchers examined NTHi in an *in vivo* model, inoculating chinchillas with either an 'ON' strain of NTHi or its corollary 'OFF' strain. Samples over the course of 22 days revealed that, on the one hand, chinchillas that received the predominantly 'ON' strain consistently yielded samples with the same 'ON' expression during infection of the middle ear. On the other hand, chinchillas that received the predominantly 'OFF' strain showed a transition during the course of the study, with later samples showing an 'ON' expression as well.

This transition demonstrates how phase variation, a natural ability to switch between phenotypes, can convey fitness advantages in an infecting population. However, the authors emphasize, by studying these phenotypes researchers might eventually define a stable immunological target for future treatments of NTHi. The authors even noted that phase variation of *modA* influences the expression of some proteins that are candidate targets for vaccine development.

"Through this research we have been able to understand the lifestyle of the bug and its adaptation to us as hosts," Jennings summarized in a press release. "We now have a better idea of which surface proteins are good targets for vaccine development."

Gregory D. Larsen