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Addiction Behavior in One Protein

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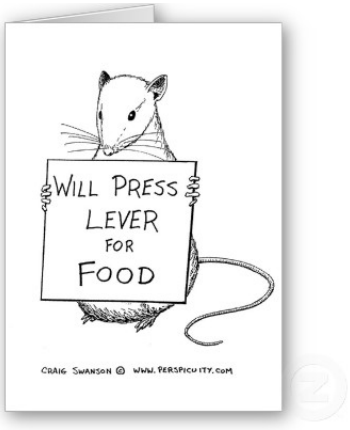

Addiction is a hard disease to define. We all understand in a general sense what addiction to drugs or sex or food means or looks like, but when it comes to an explicit definition, even the experts struggle. In the DSM-IV, the manual for psychiatric disease, addiction is bifurcated into “substance abuse” and “substance dependence,” and anyone who shows a handful from a grab bag of symptoms (such as “failure to fulfill major obligations,” “withdrawal,” and “large amounts over a long period”) meets the diagnosis.

So imagine trying to model this complex behavior in animals, where experiments can attempt to unravel some of the brain changes that underlie addiction. Not easy. But one DSM-IV symptom may offer a clue - “continued use despite adverse consequences.” Addicts appear to find their chosen drug to be much more *important* than other people, and are willing to put up with more adversity in order to acquire and take the drug, fighting through physical illness and loss of work, home, and family. You can’t threaten a lab rat with losing his job, but you can measure how important the drug is to an animal through self-administration, measuring how many times the rat will press a lever to receive a hit of drug.

That model has been the central approach in the behavioral addiction laboratory of Paul Vezina, Ph.D. (below, left), Professor of Psychiatry and Behavioral Neuroscience at the University of Chicago Medical Center. Rats in Vezina’s lab are given a series of injections of cocaine or amphetamine over the course of a couple weeks to induce

sensitization, a well-studied phenomenon where the behavioral effects of the drug - running around, in rats - increases after multiple exposures. Sensitized rats will work much harder for drug, sometimes hitting a lever as many as 1000 times for just one single burst of amphetamine, suggesting a similar imbalance of motivation as one sees in addicted humans.

“The drug short circuits your system and makes your system sensitized, which is associated with the pathological pursuit of this behavior - that’s the problem,” Vezina said. “With alcohol, there’s no problem having a glass of wine with dinner, but there’s a problem having three bottles. Our argument is that exposure to the drug in select individuals will lead to a sensitization of these pathways and some behaviors.”

The hunt, then, is focused on determining what changes in the brain to produce this dramatically exaggerated motivation for drug. In a new paper, published earlier this month in The Journal of Neuroscience (30:939-949, 2010) Vezina’s laboratory presents a series of intriguing experiments that demonstrate just one molecule can push a rat into becoming a furry model of human addiction, hammering away at the drug-lever to the exclusion of all other activity.

The experiments focus on a region of the brain called the nucleus accumbens, part of a structure named the basal ganglia. Activity in the basal ganglia is responsible for motivated behavior, the pursuit of things organisms need to survive and reproduce such as food, water, and sex. Most drugs known to be addictive in humans toy with a neurotransmitter in the nucleus accumbens called dopamine

“The basal ganglia consists of pathways that are very primitive. We share them with all mammals, and they’re pretty well conserved,” Vezina said. “These are very primitive systems in the brain that are still there for a reason. Addicts exploit certain drugs because the drugs have direct access to dopamine pathways. But we need these pathways to survive, and if you play with that pathway, funny things are going to happen to your behavior. ”

Exposure to drugs sensitizes the pathways of the basal ganglia, leading to sensitized behavior. But how? Previous experiments have looked at what changes after repeated exposure to drug - dopamine release is enhanced, and certain cellular messengers are increased. One such messenger comes with the unwieldy name of calcium/calmodulin-dependent protein kinase II, helpfully shortened to CaMKII in print and “cam-kinase” in conversation (should you ever need it at a cocktail party). A sensitizing regimen of drugs such as cocaine and amphetamine will increase the amount of CaMKII, and inhibitors of the protein block the increased locomotion and drug-taking seen in sensitized animals. The activity of CaMKII also makes it intriguing; as a kinase, the protein can turn on and off several other proteins mediating a strong and long-lasting change to function of the basal ganglia.

But just how important is CaMKII to sensitization? To answer that question, Jessica Loweth and other members of the Vezina lab attached the kinase to an interesting vehicle for delivery into the brain: the herpes virus. Merely putting CaMKII into the brain permanently wouldn't appropriately recreate the changes seen after drug exposure, where CaMKII is elevated in the 4 days after drug but back to normal a week later. In the same way that herpes sores will appear for a few days before going away, the herpes virus can be used to transiently express an attached protein. So Loweth and colleagues intracranially injected CaMKII attached to herpes simplex virus into the nucleus accumbens, and waited to see how the animals would behave days and weeks later. As the researchers had hoped, the behavioral changes were remarkable: animals responded more strongly to amphetamine and showed an increased desire to self-administer the drug, even though they had never seen it previously. That suggests that merely flicking the switch of CaMKII can reproduce all the behavioral effects of sensitization, emulating some of the effects we see in addicted humans.

"The thing that still gets me today, after studying this phenomenon for years, is that you can change one protein in one tiny nucleus, and in so doing change the behavior of the whole animal," Vezina said. "That to me is still pretty awesome". The ultimate purpose of understanding the neural mechanisms of addiction, of course, is to try and find a way to cure it. In that sense, further experiments involving CaMKII have shown promise - an inactive form of the protein, called a "dead mutant" can reduce the drug-taking behavior of sensitized animals back to normal levels. That's an important demonstration, Vezina said, as it shows that there may be a way to knock down addiction without completely blocking a person's motivated behavior.

"There are many ways to get people to stop taking drugs: you can tie them down, lock them up and they'll never have drugs. You could dissect out their nucleus accumbens, but that's not a good thing," Vezina said. "The next step is to develop some kind of genetic approach where you can alter the amount of specific proteins, such as CaMKII. What research is showing to date is that would effectively reduce exaggerated responding."

***See*:** Loweth J, Singer B, Baker L, Wilke G, Inamine H, Bubula N, Alexander J, Carlezon W, Neve R & Vezina P. Transient Overexpression of -Ca2+/Calmodulin-Dependent Protein Kinase II in the Nucleus Accumbens Shell Enhances Behavioral Responding to Amphetamine. *Journal of Neuroscience, 30* (3), 939-949, 2010.

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