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Probing Question: Fishhooks of addiction

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When the American writer Theodore Roethke taught at Penn State from 1936 to 1943, he was known for three things: being a good poet, coaching the men's tennis team, and falling down drunk, perhaps the latter more than the former. Roethke, a brilliant and tortured man, knew well the seduction of drink and the agony of addiction. In his poem "Journey Into the Interior," Roethke writes, "In the long journey out of the self, / There are many detours, washed-out interrupted raw places / Where the shale slides dangerously / And the back wheels hang almost over the edge / At the sudden veering, the moment of turning."

Extend the metaphor of "the sudden veering" to an attempt to break the cycle of addiction. Roethke knew, as does every fabulous drunk, every craven meth-head, every secret smoker, every last heroin addict that "the shale slides dangerously." Even with the best rehab clinics and support groups, addicts find that slipping back into the warm, dark womb of addiction is far easier—and much more pleasurable—than crawling out of it.

Depending on which study you read, the relapse rate for drug and alcohol addiction ranges from 50 to 90 percent. These numbers do not surprise Kyung-An Han, associate professor of biology, whose primary work seeks to understand how molecules in the brain mediate behavior. Last winter, Han delivered the lecture, "Addiction: A Bad Case of Good Memory," in the ongoing Frontiers of Science series sponsored by the Eberly College of Science, in which she explored addiction as an involuntary form of learning and memory. Han argues that addiction has nothing to do with willpower. She says, "Addiction is a problem of the brain that can be chronic and progressive. It is not a moral issue. Our behavior is largely controlled by brain function."

Journey to the Center of the Brain

Back in the 1980s, before first-graders knew what PET scans were and "dopamine" and "serotonin" became household words, the Partnership for a Drug-Free America, launched a massive anti-drug campaign that used a fried egg to symbolize "your brain on drugs." We know today what actually causes the frying.

Deep in the heart of the brain, at its center where the brain stem attaches, lies the ventral tegmental area (VTA), which is made up of neurons that receive information from other parts of the brain, much of it having to do with how well human needs are being satisfied. The chemical messenger dopamine sends this information to the nucleus accumbens in the forebrain, directly in front of the VTA. Together, these two brain areas blaze the brain reward pathway. Paradise on earth begins in this part of the brain. Pleasure is mediated by dopamine, which, Han says, "is key to our survival as a species."

Dopamine is a main player in this part of the brain. Natural rewards, like food and sex, says Han, increase dopamine levels in the nucleus accumbens, which receives information from the VTA. Artificial rewards, particularly drugs like cocaine, amphetamines, methamphetamines, and methylphenidates (e.g. Ritalin), wreak havoc in the brain by mimicking the chemical structure of dopamine and binding to the transporter dopamine normally binds to.

Normal, healthy brain communication occurs when a neuron sends an electrical signal from the cell body through its branching dendrites to the neuron's axonal terminals, where it crosses the synapse to another neuron. Once the signal is received, it needs to be terminated so that other signals can get through. Cells control this process by using a transporter, a reuptake molecule that's in the "sender" neuron. When the dopamine molecule does its job in a healthy brain, it binds to dopamine receptors in the "receiver" neuron to transmit the signal. When the task is done, the dopamine is reuptaken by the dopamine transporter in the "sender" neuron so it can be used again.

Drugs block the transporter, which basically floods the area with dopamine, which then continuously activates the receptor, thus enhancing pleasure. "That's why people feel euphoria when they take drugs," says Han. "The reward pathway is the central pathway of many drugs," including heroin, alcohol, and nicotine."

The bottom line is that drugs make the brain feel good, but there's a fine line between intoxication and toxicity. When the brain is flooded with drug-induced dopamine, it compensates by reducing the number of dopamine receptors among the neural receptors, as well as reducing glucose production, the main energy source for the brain. Ultimately, the entire brain function slows. The prefrontal cortex, the executive area responsible for planning and remembering, muddies. Synapses aren't firing the way they should. Memory and emotion are deleteriously affected. All that excess dopamine fries the receptor circuits in a flash dance of frenzy—then, the natural receptors shrivel up. This is your brain on drugs.

Addiction and Memory

In her work at Penn State, Han began using fruit flies to study memory and learning. Drosophila melanogaster makes an excellent model for conditioning studies, Han explains, as it has a sophisticated central nervous system whose molecular components and neural communications are similar to those in humans. By using different scents associated with either a slight electric shock or a sucrose reward, Han's team, made up of graduate and undergraduate students, easily constructed aversive and appetitive (avoidance and attraction) conditioning scenarios to study the underlying molecules responsible for learning and memory. Briefly, flies learned to avoid the smells linked with shocks and seek out the ones that yielded sugar. Her team studied neurotransmitters, dopamine and octopamine, which is analogous to the neurotransmitter norepinephrine in humans (with epinephrine, it signals the fight-or-flight response).

"We knew from prior studies, those molecules are important, and we are really getting into the mechanisms of how these dopamine and octopamine systems actually mediate this aversive vs. appetitive conditioning," says Han. As it turns out, "There is an exact analogy with [what happens in the brains of] drug addicts."

Instead of a particular smell that triggers avoidance or attraction in fruit flies, Han, interested in understanding the molecules and mechanisms that underlie the association of environmental cues with behavior, suggests that visual cues like a coke mirror or a beer bottle may work as a conditioning stimuli. And this could be a powerful trigger for drug addicts or alcoholics. "In learning and memory, this particular process is enhanced in people in who have been taking drugs for a long time," she says. "We became interested in asking the question, 'Are there any common pathways that mediate the natural learning and memory process vs. the drug-induced learning and memory process?' That's how we got into studying alcohol and cocaine."

The brain likes dopamine. No, the brain loves dopamine. Pointing to the seminal study by Olds and Milner that first identified the brain reward pathway in 1954, Han says that rats prefer to have the VTA—starting point of the reward pathway—stimulated over receiving food or having sex. And dopamine is not only the magic neurotransmitter that makes the reward pathway possible but also the neurotransmitter that the brain produces in abnormal numbers with the intake of certain drugs and alcohol. People who need a cigarette or cocktail to calm their nerves are actually being pacified by a sudden rush of chemicals in the brain's happy place. Thus, Han began to understand the molecular basis for what the brain loves, which is not necessarily the most healthy thing for the rest of the body, and how the fruit-fly brain learns and remembers that which it loves—dopamine and octopamine.

Sex and the Single Fly

Working on the hypothesis that enhanced behavior triggered by repeated experience requires memory, Han and her team began giving ethanol to the flies on a daily basis to extend their memories about ethanol experience. Along the way, the team made some surprising discoveries that had more to do with behavior than memory—and some outrageous behavior at that. The study, published in the January 2, 2008 issue of the scientific journal PLoS One, is a groundbreaking look at the effects of chronic alcohol exposure in fruit flies. (Similar fruit-fly studies around the world have only looked at short-term exposure.) And, as in humans, excessive alcohol intake in fruit flies is not pretty.

In wild-type flies Han and her team found that ethanol-intoxicated male flies lost their sexual inhibitions, and that this disinhibited behavior intensified with the repeated experience of ethanol. With chronic alcohol (i.e., ethanol) consumption, the drunken male flies, who normally only court females, began courting other males ... to no avail.

Using transgenic flies, Han blocked dopamine neurotransmission by raising the temperature to 32 degrees C, which temporarily disables the effect of dopamine. These flies, even when given large doses of ethanol, had no interest in other male flies. Han says. “This result suggests that dopamine is a key mediator of ethanol-induced inter-male courtship.”

No one expected to witness this behavior. Says Han, “People thought ethanol could stimulate sexual arousal in humans, but there never was a biological or physiological model to support it. People thought it was more psychological, but flies don’t normally make the assumption that because I drink it will be okay if I court another male. This increase in sexual arousal is totally physiological. It’s quite a fascinating model to understand the physiological basis.”

And while her work is open to parody of beer goggles and frat boys, Han says that her team’s studies show this: there is most definitely a connection between addiction, inhibition, and dopamine. While the brain loves the gush of addiction-induced molecules, we humans, are still creatures of choice. Says Han, “The way we are defined as humans is that we have evolved brains with good inhibitory systems. Humans can choose to not drink or not drive and drink.”

Use these evolved brains, she suggests. Make good choices before the fish hooks of addiction grab hold of your neurotransmitters and don’t let go. Rather than settle down for a night of pinot noir at the end of the day, go for a run. Excite the brain reward pathway with the body’s own unfettered dopamine supply. “Everyone wants to seek pleasure,” she says, “but the best way to do it is to boost the pleasure center naturally. Use science.”

Source: By Gigi Marino, Research/Penn State

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