Teaching the Brain to Take Drugs

Activation of the brain's glutamate circuitry may contribute to the learning of addictive behavior. If so, drugs that block glutamate activity may help addicts kick their habit

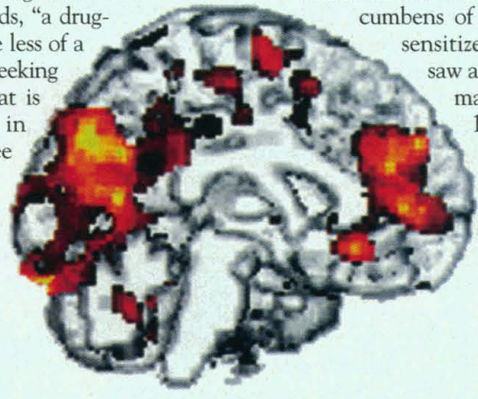
To the brain, an addictive drug is an evil tutor. Its lesson: The brain should want more of the drug and should direct the body to get it—whatever the costs. That lesson rarely gets forgotten, as every relapsed addict knows. Now, recent work is implicating a new player in the addictive learning experience: the neurotransmitter glutamate, which is already thought to be key to more normal learning.

Until the past few years, neuroscientists studying addiction have usually focused on another neurotransmitter, dopamine, partly because they found that all addictive drugs cause a surge of dopamine in the brain's reward center, the nucleus accumbens. By capturing the brain's attention, this seems to reinforce drug-seeking behaviors (*Science*, 3 October 1997, p. 35). Recently, though, several lines of evidence have pointed to glutamate as a different kind of teacher's helper for addictive drugs. While bursts of dopamine elicited by the drugs attract the brain's attention, modifications in glutamate signaling seem to produce more stable changes in the brain that lead to compulsive drug-seeking.

Researchers have found, for example, that blocking glutamate transmission prevents behavioral sensitization in rats. In sensitization, repeated doses of amphetamine or cocaine make the animals more and more frantic, causing them to run faster around their cages or engage in purposeless motions like turning their heads back and forth. Such behavior, thought to reflect changes in the brain, may parallel the increasing anxiety and drug craving that humans feel after repeated hits of amphetamine or cocaine. Scientists have also identified lasting cellular and molecular changes that seem to increase activity in the brain's glutamate circuitry in animals given cocaine. Some of these glutamate circuits may be reactivated during drug cravings—a theory buttressed by brain imaging studies in humans.

The notion that glutamate plays such a critical role in drug addiction "is a really exciting, new idea," says behavioral neuroscientist Ann Kelley of the University of Wisconsin School of Medicine in Madison. Adds neuroscientist Peter Kalivas of Washington State University in Pullman: "People are pretty high on glutamate right now."

They are euphoric partly because the work suggests that compounds that interfere with glutamate signaling could block the intense drug cravings addicts feel during withdrawal or when they see drug-related objects—cravings that often lead to relapse. "A key problem in addiction is relapse," says Barbara Herman of the National Institute on Drug Abuse in Rockville, Maryland, who chaired a meeting on glutamate last month at the National Institutes of Health.* For example, one study showed that individuals had "about an 80% chance of slipping up within the first year" after leaving an opiate treatment program, she says. But "with glutamate antagonists," Herman adds, "a drug-related cue might have less of a potential to elicit drug-seeking behavior"—a hope that is already being tested in some human trials (see sidebar).



SOURCE: S. GRANT, K. BONSON, E. LONDON *ET AL.*

Glutamate high. In cocaine abusers, drug-related stimuli increase the activity (indicated by red color) in areas such as the frontal cortex that release glutamate onto the brain's reward centers.

Stopping the frenzy

For decades, neuroscientists have noticed anatomical clues that point to glutamate as one of dopamine's partners in teaching the sinister lessons of addiction. They found, for example, that glutamate-releasing neurons originating in the brain's thinking areas, including the cerebral cortex, the hippocampus, and amygdala, release glutamate onto neurons in the nucleus accumbens.

But the first direct evidence that glutamate plays a role in addiction didn't come until the late 1980s, when Ralph Karler and his colleagues at the University of Utah School of Medicine in Salt Lake City showed that a drug called MK-801, which prevents glutamate from acting through one of its key receptors, the *N*-methyl-D-aspartate (NMDA) receptor, prevents rats and mice from becoming sensitized to cocaine and amphetamine.

In the early and mid-1990s, a team led by Marina Wolf at The Chicago Medical School in North Chicago confirmed and extended Karler's findings. These researchers discovered that drugs that block various types of glutamate receptors prevent sensitization to amphetamine in rats, as do lesions of the prefrontal cortex, the home of many neurons that discharge glutamate into parts of the reward circuit. "You need glutamate to get sensitization," Wolf concludes, "and that means sensitization has a lot in common with other forms of learning."

Kalivas agrees. When he and his colleagues measured concentrations of the neurotransmitter in the nucleus accumbens of rats that had been sensitized to cocaine, they saw a large jump in glutamate levels, to 50% to 100% above normal. "Only the animals that developed sensitization showed changes in glutamate transmission," Kalivas says. "So glutamate is what gets recruited for the long-term changes" that lead to sensitization. If sensitization is a good model of drug craving, enhanced glutamate activity in the brain might be at the root of drug-seeking behavior.

Indeed, that idea is supported by as-yet-unpublished results from Kalivas's team. In these experiments, the researchers taught rats to press a lever for cocaine and then after 3 weeks replaced the cocaine with a plain salt solution. That caused the animals to stop pressing the lever—until they were given a compound that mimics glutamate action at another of its receptors, called the AMPA receptor. Then the rats began pounding on the lever that once produced cocaine as if they were craving the drug. "We believe that repeated exposure to a drug activates glutamate transmission," says Kalivas. When the glutamate system is reactivated—as it might be by some reminder of the drug or the drug itself—"this contributes to feelings of craving and paranoia."

The same may happen in humans. Two years ago, for example, neuroscientists Steven Grant, Edythe London, and their colleagues at the National Institute on Drug Abuse in Baltimore, Maryland, and Yale University

* The meeting, "The Glutamate Cascade: Common Pathways of Central Nervous System Disease States," was held 3–5 May (www.nida.nih.gov/meetsum/glutamate/index.html).

Pills to Help Keep You Clean

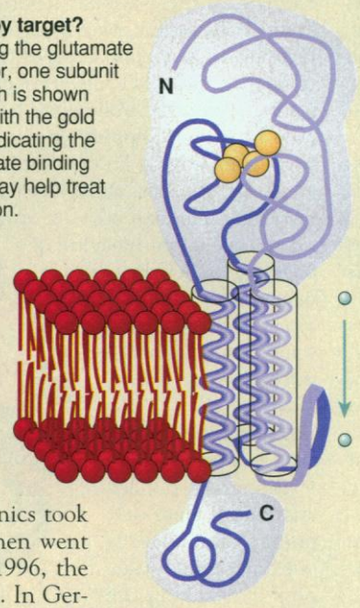
As neuroscientists link changes in the brain's glutamate system to the learning and maintenance of addictive behavior (see main text), they are finding hints that drugs that interfere with glutamate transmission might be used to treat addiction. "There are a number of promising compounds on the horizon," says Charles Inturrisi of Cornell University Medical College in New York City, whose lab is among those doing the work.

So far, a drug called acamprosate, which has been approved for treating alcoholism in Europe and is in clinical trials in the United States, has shown the greatest promise. Originally designed to treat epilepsy, acamprosate was being tested for its ability to quell alcohol-induced seizures in the early 1980s when researchers noticed that trial subjects seemed to relapse less often than controls. Pilot studies in France bolstered this idea, but nobody knew how the compound worked until neuropharmacologist Walter Zieglgänsberger and his colleagues at the Max Planck Institute of Psychiatry in Munich, Germany, showed in the late 1980s and early 1990s that acamprosate blocks the ability of glutamate to stimulate electrical activity in both rat cortical neurons and in the cortexes of anesthetized rats.

Meanwhile, investigators in 10 European countries began a large-scale clinical trial of acamprosate as a treatment for alcoholic relapse. In the trial, 4000 patients who had been weaned from alcohol at local clinics took either a placebo pill or acamprosate for 1 year and then went without treatment for a second year. By the end of 1996, the results, which were similar in all 10 countries, were in. In Germany, for example, 39% of patients who had received acamprosate were still abstinent after a year of follow-up, compared with 17% of controls.

For at least some subjects, the drug, which seems to have no serious side effects, diminishes craving for alcohol: "With acamprosate, patients tell you they don't even think about alcohol," Zieglgänsberger says. What's more, the drug's effects apparently last. Two-year follow-up data from the German portion of the trial still show a lower relapse rate among the patients who took acamprosate.

Scientists don't know how acamprosate combats alcoholism, but recent work indicates that a dampening of glutamate-triggered activity in cortical neurons—which might reduce craving—is just part of the story. This spring, the Munich team along with George Koob, George Siggins, and their colleagues at The Scripps Research Institute in La Jolla, California, showed that acamprosate actually increases glutamate's activation of neurons in two other rat brain areas, the hippocampus and nucleus accumbens. It's possible, Zieglgänsberger suggests, that during withdrawal, neurons in these areas are abnormally quiet and acamprosate helps enliven them, thereby reducing withdrawal symptoms that can trigger drug cravings.



Therapy target? Blocking the glutamate receptor, one subunit of which is shown here with the gold balls indicating the glutamate binding site, may help treat addiction.

SOURCE: TIM GREEN/SALK INSTITUTE

Researchers discovered acamprosate's promise in treating addiction accidentally, but they are also looking more systematically for glutamate inhibitors. One hurdle is that widespread blockage of brain glutamate receptors can impair learning and memory as well as produce hallucinations; the drug PCP is a powerful glutamate inhibitor. But researchers have identified substances that loosely bind to the NMDA glutamate receptor without completely crippling it.

One such compound is dextromethorphan, a medication approved for use in over-the-counter cough syrups. Luigi Pulvirenti's team at Scripps and the Claude Bernard Neuroscience Foundation, also in La Jolla, has shown that giving rats dextromethorphan after they'd been trained to self-administer cocaine can curtail cocaine-seeking behavior. And Inturrisi and his colleagues have found another clue that dextromethorphan blunts addiction: In mice, it blocks the development of, and even reverses, morphine tolerance, in which people need ever more of the drug to feel its effects.

In addition, researchers are studying other NMDA-receptor blockers as potential antidotes to morphine tolerance and perhaps opiate dependence. If these efforts pan out, research on glutamate's role in addiction may someday help hundreds of thousands of people kick their drug habits. –I.W.

School of Medicine in New Haven, Connecticut, rated the cocaine cravings reported by 13 addicts and five controls who watched films of people using both neutral objects and drug-associated items such as glass pipes and razor blades. At the same time, the researchers used positron emission tomography to scan the subjects' brains.

The researchers found that the degree of craving in the addicts paralleled the intensity of neural activity in the frontal cortex and the amygdala, brain regions that release glutamate in the nucleus accumbens and serve learning and memory functions. Thus, cognitive brain structures that rely heavily on glutamate seem to play a role in the cravings elicited by external cues.

Changing the brain

The cellular and molecular changes in the brain's glutamate system that might underlie these changes in activity are now coming to light. At the glutamate meeting, Luigi Pulvirenti of The Scripps Research Institute and the Claude Bernard Neuroscience Foundation, both in La Jolla, California, described experiments in which his team first taught rats to press a lever for either cocaine or food and then measured how much neural activity in the nucleus accumbens they could elicit by stimulating fibers from the hippocampus that feed it glutamate.

As the rats were first learning to work for cocaine, Pulvirenti says, he and his colleagues found "an incredibly enhanced" neuronal response in the accumbens compared to rats that either worked for food or received cocaine passively. The result is what would be expected if glutamate mediates the animals' learning that they can get cocaine by pressing the lever. "These changes in synaptic efficacy may be part of the early neuronal events that later lead to drug-seeking behavior," Pulvirenti says.

Part of the enhanced responsiveness of the nucleus accumbens neurons might be due to the large jolts of glutamate discharged there when the animals were given cocaine. But Kalivas's team has seen evidence of a more permanent change in cocaine-treated rats that might also contribute to the effect: an increase in the number of protein components for glutamate receptors in neurons of

the nucleus accumbens. The implication is that the brain builds more glutamate receptors in that region as cocaine addiction takes hold.

Whether the same happens in amphetamine addiction is less clear, because Wolf and her colleagues found large decreases in the proteins forming the AMPA glutamate receptor in nucleus accumbens neurons in rats sensitized to amphetamine. Still, says Wolf, the data do show "that there are adaptations in glutamate transmission in response to chronic exposure to [both] drugs."

Sensitized animals are thought to be especially valuable models of addiction to cocaine and amphetamine—stimulants whose rewarding properties seem to be the main impetus for cravings and repeated drug use. But for other drugs, such as opiates, avoiding withdrawal symptoms is thought to be at least as strong a driver for continued use as is seeking a high. Inhibitor studies have implicated glutamate's brain-sculpting effects in this kind of addiction as well. It seems to play a role in both opiate dependence, in which withdrawal symptoms develop when the drugs are taken away, and tolerance, in which an individual needs more of the drug with continued use to experience the desired effects.

In 1991, for instance, Keith Trujillo and Huda Akil at the University of Michigan, Ann Arbor, showed that the NMDA antagonist MK-801 could prevent rats from becoming either tolerant to morphine or dependent on it. And in 1993, neuropharmacologist Charles Inturrisi of Cornell University Medical College in New York City, with then-postdoc Paul Tiseo, discovered that another NMDA antagonist, called LY274614, could even reverse tolerance to morphine in rats. This suggested that such antagonists might help addicts or people with chronic pain who have developed opiate dependence or tolerance.

Although many of the molecular and cellular details of glutamate's influence on addiction remain to be worked out, it's now clear that glutamate does mediate many of the lessons taught by drugs. In doing so, it creates lasting memories by changing the nature of the conversations between neurons—a phenomenon neuroscientists call neuronal plasticity. Says Pulvirenti: "The plasticity that occurs during drug addiction most likely depends on glutamate transmission."

Of course, plasticity is also the basis of everyday learning and memory. Thus, the same neurotransmitter may hold the key to both preserving the good memories and erasing those planted by the tutors of addiction.

–Ingrid Wickelgren

Additional Reading

S. Grant *et al.*, "Activation of memory circuits during cue-elicited cocaine craving," *Proceedings of the National Academy of Sciences* **93**, 12040 (1996).

B. H. Herman and C. P. O'Brien, "Clinical medications development for opiate addiction: Focus on nonopioids and opioid antagonists for the amelioration of opiate withdrawal symptoms and relapse prevention," *Seminars in Neuroscience* **9**, 158 (1997).

R. C. Pierce *et al.*, "Repeated cocaine augments excitatory amino acid transmission in the nucleus accumbens only in rats having developed behavioral sensitization," *The Journal of Neuroscience* **16**, 1550 (1996).

R. Spanagel and W. Zieglgänsberger, "Anti-craving compounds for ethanol: New pharmacological tools to study addictive processes," *Trends in Pharmacological Sciences* **18**, 54 (1997).

ASTRONOMY

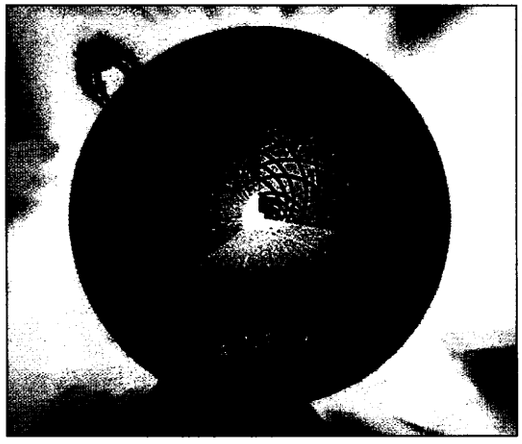
Seeking the Sun's Deepest Notes

The sun plays a silent symphony. It reverberates with oscillations that shake its surface and cause subtle frequency shifts in light from the glowing gases. These oscillations carry clues to the sun's interior, and astronomers have been watching them avidly with a network of telescopes called the Global Oscillation Network Group (GONG) and a space-based observatory called SOHO (*Science*, 31 May 1996, p. 1264). But so far, the sun's deepest notes—slow pulsations that stir its very core—have eluded them. At a workshop early this month in Boston, researchers discussed new strategies for identifying these deep undulations and weighed one claim of a candidate detection.

The solar oscillations studied so far are acoustic modes, which resemble sound waves. Generated by turbulence near the surface of the sun, they penetrate the interior and are deflected back toward the surface by the increase in density with depth. These so-called p-modes, which cause patches of the sun's surface to rise and fall over periods of from three to several dozen minutes, have helped solar physicists map the sun's density structure and interior flows (*Science*, 5 September 1997, p. 1438).

But p-modes don't penetrate to the core, where the sun's fusion power plant seethes. To probe those depths, astronomers need to pick up gravity or g-modes, in which large masses of gas heave up and down, driven by buoyancy. Such waves should have longer periods than the p-modes. "Thirty-six minutes ... divides g-modes from p-modes," says Richard Bogart of Stanford University.

The exact frequencies and patterns of g-modes would help astronomers answer such questions as the rotation rate of the sun's core, which would affect deep mixing and the sun's nuclear processes. But the g-modes are thought to be weak and hard to pick out of the noise. "There are so many peaks in the power spectrum, and to tell which peak is real or just noise is almost impossible at this stage," says Jørgen Christensen-Dalsgaard of Århus University in Denmark.



SOURCE: SOHO

Plumbing the depths. G-modes stir the sun's core.

Alan Gabriel of France's Institute of Space Astrophysics near Paris reported at the meeting, however, that he may have caught a glimpse of g-modes in SOHO data. "I daringly announced two possible g-mode candidate frequencies. Emphasis is on the word candidate," he adds. Most astronomers *Science* talked to are not convinced that the reported signal—two peaks with periods of 66 and 75 minutes—is the real thing, however. "It's far too early to say whether those are really detections or just random peaks," says Bogart, who adds that it would take at least three or four peaks satisfying the expected frequency relationships to convince him.

Thierry Appourchaux of the European Space Research and Technology Centre in Noordwijk, the Netherlands, thinks he has a way to find stronger, more convincing peaks: Look at the limb of the sun—its visible edge—rather than the center of the disk. "At the solar limb, the same perturbation can give a three to four times stronger signal," he says, explaining that at the limb one can track the motions of higher layers of gas, where the density falls and the amplitude of the waves grows.

Because of instrument limitations, SOHO can't track motions at the solar limb. But Appourchaux is part of a group that will try this strategy for picking up the sun's low notes with PICARD, a small solar observatory that France will launch in 2002.

–Alexander Hellemans

Alexander Hellemans is a science writer in Naples.