Marijuana: Harder Than Thought?

Contrary to the popular view that marijuana is a relatively benign drug, new evidence suggests its effects in the brain resemble those of "hard" drugs such as heroin

For decades, policy-makers have debated whether to legalize marijuana. Compared to drugs such as heroin and cocaine, many people—scientists and teenagers alike—consider marijuana a relatively benign substance. Indeed, there was little evidence to indicate that it is addictive the way those drugs are. But now, two studies in this issue demonstrate disturbing similarities between marijuana's effects on the brain and those produced by highly addictive drugs such as cocaine, heroin, alcohol, and nicotine.

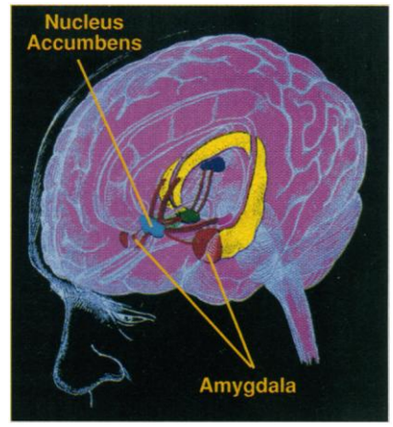
In one study, which appears on page 2050, a team of researchers from the Scripps Research Institute in La Jolla, California, and Complutense University of Madrid in Spain trace the symptoms of emotional stress caused by marijuana withdrawal to the same brain chemical, a peptide called corticotropin-releasing factor (CRF), that has already been linked to anxiety and stress during opiate, alcohol, and cocaine withdrawal. And on page 2048, Gaetano Di Chiara of the University of Cagliari in Italy and his colleagues report that the active ingredient in marijuana—a cannabinoid known as THC—results in the same key biochemical event that seems to reinforce dependence on other drugs, from nicotine to heroin: a release of dopamine in part of the brain's "reward" pathway.

Together, the two sets of experiments suggest that marijuana manipulates the brain's stress and reward systems in the same way as more potent drugs, to keep users coming back for more. "These two studies supply important evidence that marijuana acts on the same neural substrates and has the same effects as drugs already known to be highly addictive," says David Friedman, a neurobiologist at Bowman Gray School of Medicine in Winston-Salem, North Carolina. They also, he adds, "send a powerful message that should raise everyone's awareness about the dangers of marijuana use."

But the results may have a more hopeful message as well, because they may guide scientists in devising better strategies for treating marijuana dependence, for which some 100,000 people in the United States alone seek treatment each year. For instance, chemicals that block the effects of CRF or even relaxation exercises might ameliorate the miserable moods experienced by people in THC withdrawal. In addition, opiate antagonists like naloxone may, by dampening dopamine release, block the reinforcing properties of marijuana in people.

Scripps neuropharmacologists Friedbert Weiss and George Koob first began thinking that stress systems might be involved in drug dependence in the early 1990s, after noticing that withdrawal from many drugs produces an anxious, negative disposition that resembles an emotional response to stress. They reasoned that drug withdrawal might recruit the same brain structures and chemicals that are involved in the stress response. Because Koob's team had associated emotional stress with the release of CRF in a brain structure called the amygdala, they thought that drug withdrawal might also trigger CRF release.

Beginning in 1992, the Scripps researchers amassed evidence showing that this is indeed the case. First, Koob and his colleagues found that injecting chemicals that block CRF's effects into the amygdalas of alcohol-dependent rats reduces the anxiety-related symptoms, such as a reluctance to explore novel settings, that develop when the animals are taken off alcohol. Then in 1995, Weiss, Koob, and their colleagues showed that CRF levels quadruple in the amygdalas of rats during the peak of alcohol withdrawal.



Targets. The amygdala and nucleus accumbens are two brain areas where marijuana appears to have addictive effects.

After similar experiments demonstrated that elevated CRF underlies emotional withdrawal from opiates and cocaine, Weiss, Koob, and M. Rocío Carrera of Scripps, along with two visiting Spanish scientists, Fernando Rodríguez de Fonseca and Miguel Navarro, set out to investigate whether CRF might mediate the stressful malaise that some long-term marijuana users experience after quitting.

The researchers injected a synthetic cannabinoid into more than 50 rats once a day for 2 weeks to mimic the effects of heavy, long-term marijuana use in humans. Normally, marijuana withdrawal symptoms develop too gradually to be recognized easily in rats, because the body eliminates THC very slowly. But the researchers were able to produce a dramatic withdrawal syndrome lasting 80 minutes by injecting the rats with a newly developed drug that counteracts THC. The drug does this by binding to the receptor through which cannabinoids exert their effects.

The group found that the cannabinoid antagonist greatly increased the rats' anxiety, as measured in a standard behavioral test, and exaggerated such signs of stress as compulsive grooming and teeth chattering during withdrawal. What's more, when the scientists measured CRF levels in the rats' amygdalas, they found that rats in withdrawal had two to three times more CRF than controls not given the antagonist, and that the increase paralleled the apparent anxiety and stress levels of the rats.

The results, experts say, provide the first neurochemical basis for a marijuana withdrawal syndrome, and one with a strong emotional component that is shared by other abused drugs. "The work suggests that the CRF system may be a part of a common experience in withdrawal—that is, anxiety," says Alan Leshner, director of the National Institute on Drug Abuse. A desire to avoid this and other negative emotions, Weiss suggests, may prompt a vicious cycle leading to dependence.

But withdrawal is just one component of addiction. Addictive drugs also have immediate rewarding, or reinforcing, effects that keep people and animals coming back for more. The drugs produce these effects, scientists believe, by hijacking the brain's so-called reward system. A key event in the reward pathway is the release of dopamine by a small cluster of neurons in a brain region called the nucleus accumbens. Researchers think the dopamine release normally serves to reinforce behaviors that lead to biologically important rewards, such as food or sex. Addictive drugs are thought to lead to compulsive behavior because they unleash a dopamine surge of their own.

But no one had been able to show convincingly that marijuana could induce that telltale dopamine rush, until Di Chiara and his colleagues put THC to the test. When the Cagliari team infused the cannabinoid into a small group of rats and measured dopamine levels in

the nucleus accumbens, they found that the levels jumped as much as twofold over those in the accumbens of control rats infused with an inactive cannabinoid. The magnitude of the surge was similar to what the researchers saw when they gave heroin to another set of rats.

Further work confirmed that cannabinoids, rather than other factors such as the stress of being handled by the experimenters, were responsible for the dopamine release. For example, the researchers observed no dopamine increase in animals who were given a receptor blocker before the THC.

Then Di Chiara and his colleagues found an additional parallel between THC and heroin. They showed that naloxone, a drug that blocks brain receptors for heroin and other opiates, prevents THC from raising dopamine levels, just as it does with heroin. This indicates that both marijuana and heroin boost dopamine by activating opiate receptors. Marijuana, however, presumably does so indirectly, by causing the release of an endogenous opiate: a heroinlike compound made in the brain. "Marijuana may provide one way of activating the endogenous opiate system," explains Di Chiara.

Di Chiara speculates that this overlap in the effects of THC and opiates on the reward pathway may provide a biological basis for the controversial "gateway hypothesis," in which smoking marijuana is thought to cause some people to abuse harder drugs. Marijuana, Di Chiara suggests, may prime the brain to seek substances like heroin that act in a similar way. Koob and Weiss add that the stress and anxiety brought on by marijuana withdrawal might also nudge a user toward harder drugs.

More work will be needed to confirm these ideas, as well as to find out exactly how marijuana influences the stress and reward systems. For instance, nobody knows how THC interacts with neurons in the amygdala to alter the release of CRF. Nor do scientists understand the molecular steps by which THC triggers the dopamine release in the nucleus accumbens.

But despite these uncertainties, both papers should help revise the popular perception of pot as a relatively—although not completely—safe substance to something substantially more sinister. "I would be satisfied if, following all this evidence, people would no longer consider THC a 'soft' drug," says Di Chiara. "I'm not saying it's as dangerous as heroin, but I'm hoping people will approach marijuana far more cautiously than they have before."

–Ingrid Wickelgren

PALEONTOLOGY

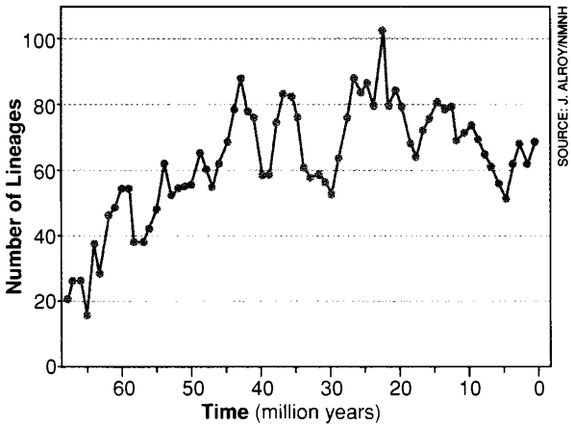
Climate-Evolution Link Weakens

We mammals have come a long way since our ancestors were a motley group of small creatures scurrying about in the shadows of the dinosaurs. We owe much of it to climate change, or so goes the conventional wisdom. Researchers have speculated that the innumerable warmings and coolings of climate pushed unfit mammals to extinction and spurred the evolution of new, better adapted species. But the best compilation of fossil evidence on mammal evolution to date now shows that climate had little effect on most of the evolutionary churnings of the past 80 million years.

"This is counterintuitive; I wanted to find a connection," says paleontologist John Alroy of the Smithsonian Institution's National Museum of Natural History. Only during a few brief periods did climate seem to drive evolution—although those periods are turning points in the history of mammals. Instead, the main determinant of the rate of evolution was the number of existing species, with new species appearing more slowly as the ark got more crowded. Alroy's results, presented at last month's meeting of the American Geophysical Union in Baltimore, are "pretty impressive," says paleontologist David Jablonski of the University of Chicago, "because it's been hard to get large-scale studies where you can look at" rates of evolution.

Alroy gained this overview by putting together a unique record of mammals. "It's the best piece of work in terms of methodology I've ever seen," says paleontologist Michael McKinney of the University of Tennessee, Knoxville. Alroy consulted 4015 lists indicating when and where 3181 North American mammal species lived during the past 80 million years. Then he adapted the record for statistical analysis by creating standard time intervals of 1 million years each and by dropping fossils from the most heavily sampled intervals, which would otherwise tend to look more diverse than sparsely sampled periods.

Alroy's final record of mammal evolution shows that mammal species were consistently scarce 80 million to 65 million years ago in the Cretaceous period, and the numbers dropped even lower during the mass extinction 65 million years ago at the time of the great impact. During the next 10 million years or so, diversity rose sharply, and then it settled into a more or less stable but higher plateau for the past 50 million years. Isotopic clues in the deep-sea sediments show numerous climate shifts over the same period, but Alroy found that most left no mark on mammal diversity.



Mammal ascent. Climate had little to do with the rise of mammal diversity after the impact 65 million years ago.

The reason mammals generally failed to respond to climate change, Alroy suspects, is that they were already adapted to an unsteady climate. Throughout the interval, cyclical variations in Earth's orbit have driven climate changes every 20,000, 40,000, and 100,000 years, he notes. The average species, surviving a couple of million years, would have to deal with repeated climate shifts.

Alroy's analysis may have put to rest the old saw about climate driving every twitch of evolution, but it could give new life to another old idea: that new species are more likely to form when ecological niches are unoccupied, as they were after the great impact catastrophe. His analysis shows that new mammal species originate at the highest rate when existing species are few.

Still, some researchers point out that climate has not been totally impotent. "It's fine that climate isn't important 95% of the time," says paleontologist Steven Stanley of The Johns Hopkins University, "but the things we have to focus on are the intervals when interesting things did happen." In fact, Alroy did find three short intervals—55, 34, and around 6 million years ago—when drastic global temperature shifts and heightened rates of diversity change did coincide. All three were times when mammal evolution took a major turn.

The diversity change Alroy identified 55 million years ago was modest, for example, but qualitatively it was a "critical interval," as Stanley has dubbed it. A host of modern mammals from primates to ungulates abruptly appeared in North America, in time with a sudden burst of warming that may have been driven by a sharp gush of greenhouse gas from the ocean's sediments (*Science*, 28 February, p. 1267). Climate may leave few marks on evolution, but they are lasting ones.

–Richard A. Kerr