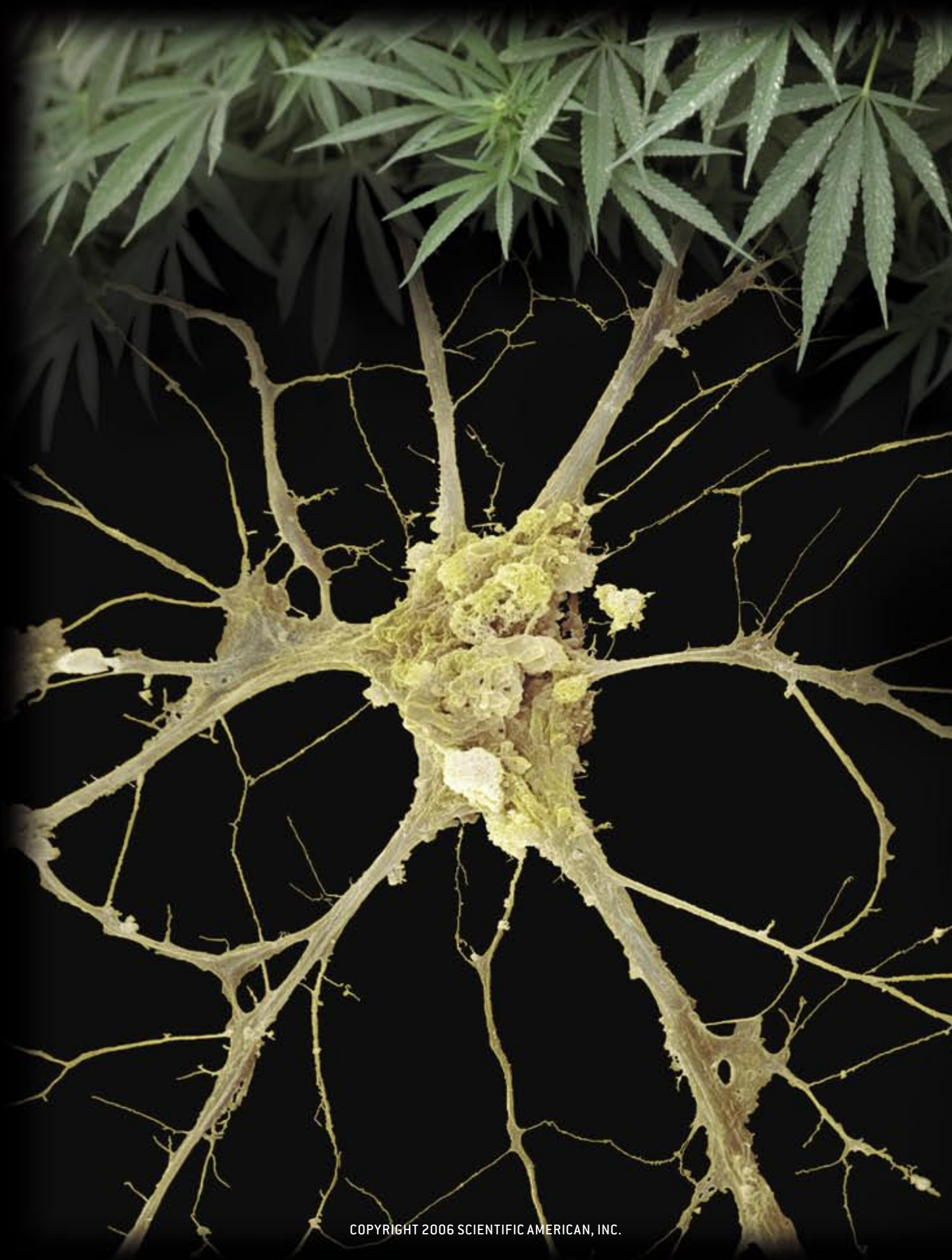


Natural HIGH

The brain produces its own "marijuana" to protect neurons, and researchers hope to exploit it to ease anxiety, obesity and addiction

By Ulrich Kraft

Chemically speaking, we are all potheads. Raphael Mechoulam of Hebrew University in Jerusalem discovered that astounding fact in 1992, and now the reasons why are finally emerging. Numerous experiments with genetically altered mice and rats have shown that when natural brain compounds, called endocannabinoids, are missing or their receptors are blocked, the animals are more susceptible to pain, cannot control their appetites, have trouble handling anxiety and are less able to cope with stress.

By fully understanding and then harnessing the endocannabinoid mechanisms, researchers are eager to devise new ways to reduce pain, calm anxiety, fight obesity, stop nicotine addiction and even treat traumatic shock and Parkinson's disease—without the unwanted side effects of smoking marijuana.

Signals in Reverse

To be precise, endocannabinoids do not mimic the effects of marijuana. It is the drug, derived from the hemp plant, that approximates the brain's endocannabinoid chemistry. A decade of study has shown that a specific receptor on certain neurons—the cannabinoid receptor 1, or CB1—binds to delta-9-tetrahydrocannabinol (THC), the active ingredient in cannabis, the dried leaf of marijuana. The same receptor binds to a class of fatty acids produced by neurons—the endocannabinoids. Mechoulam named the one he discovered anandamide—after *ananda,* the Sanskrit word for "bliss." Subsequently, Daniele Piomelli and Nephi Stella of the University of California, Irvine, found a second compound, called 2-AG, with similar characteristics. THC happens to resemble these substances closely enough that the CB1 receptors latch onto it, unleashing similar or magnified effects on the toker's brain.

> The human brain's cannabinoid system seems to fulfill multiple functions.

CB1 receptors are not everywhere in the brain—they exist in concentrated pockets in many varied locations. The distribution suggests that the human cannabinoid system fulfills multiple functions [*see box on opposite page*]. For example, numerous receptors exist in the hypothalamus, which plays a central role in controlling appetite, and in the cerebellum, which governs muscle coordination. They are also prevalent in the hippocampus, important to memory formation, as well as in the amygdala, involved in emotion and anxiety. And they are found in the neocortex, the site of such cognitive functions as speech and integration of the senses. Given the endocannabinoids' roles, it is easy to understand the classic signs of a pot smoker who is high: calm demeanor, poor motor coordination, altered sensory perceptions and an eventual attack of the munchies.

What surprised investigators, when it became clear that the endocannabinoids were communicating between neurons, was that the direction of communication occurred in reverse. When a typical neuron fires, it releases neurotransmitters that are stored near the tip of its axon. The signaling chemicals cross a small gap, or synapse, and dock with receptors on the dendrite of the next neuron, causing it to fire, and so on down the chain. The endocannabinoids, however, are rapidly synthesized in the recipient neuron's cell membrane. They cross the gap in reverse, docking at the axon [*see box on page 64*]. Neuroscientists had thought this retrograde signaling occurred only during fetal development of the nervous system.

Using mice and rats in labs, researchers slowly figured out the reason for the retrograde communication. "A neuron that has just received a message can send one right back that says, 'Stop transmitting!'" explains Andreas Zimmer, a neurobiologist at the University of Bonn in Germany who helped define the backward mechanism. "The endocannabinoids are an inhibitory feedback loop. The second neuron reports back to the sender: 'Message received. Cease firing. I got it!'"

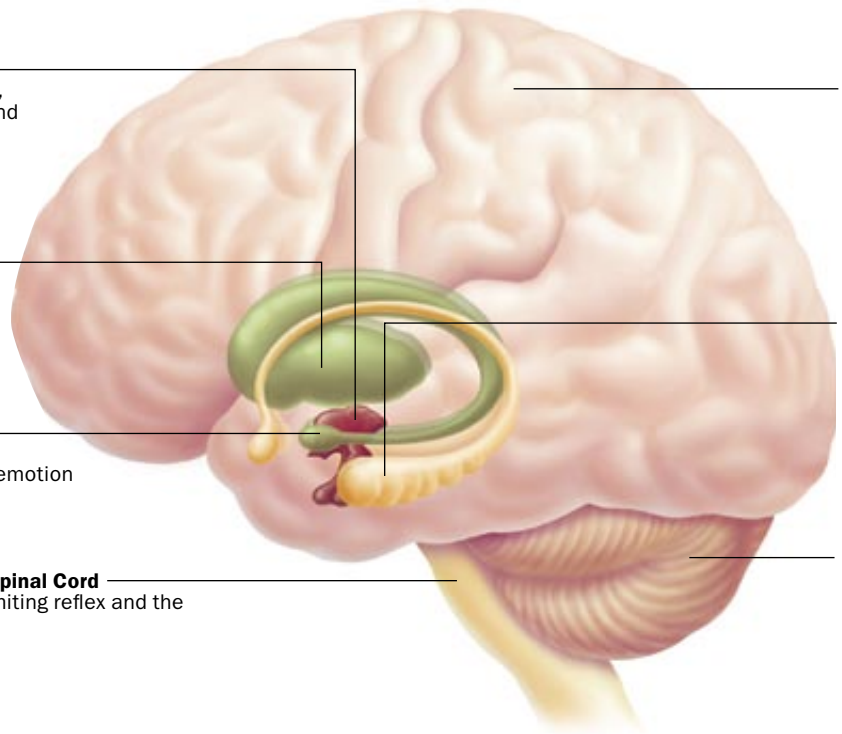
An Ancient Cure

According to Ibn Al Badri, an Arab chronicler, people knew about the inhibitory effects of hashish, also derived from hemp, at the court of the caliphs in 15th-century Baghdad. For one thing, hashish reportedly stopped the epileptic seizures in the son of a high official. Such attacks arise when neurons fire in rampant unison across the brain—

VVG *SPL Photo Researchers, Inc. (neuron);*
RIC ERGENBRIGHT *Corbis (cannabis) (preceding pages)*

Crucial Roles

Endocannabinoid receptors are concentrated in many brain regions, making them crucial to various functions. Their distribution also explains some of the classic behaviors associated with smoking marijuana and the potential payoff of drugs that mimic endocannabinoid effects for patients with severe pain or other problems.



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meaning no inhibition signal stops them. Today some epileptics can somewhat manage their attacks by smoking cannabis regularly. And yet for others, seizures worsen after this self-therapy.

Stress Protector

Still, experts now for the most part agree that the main function of the endocannabinoids is to protect neurons from excessive activity. The brain "has created a kind of emergency brake for use when needed," says Beat Lutz, a physiological chemist at the University of Mainz in Germany who has also helped elucidate endocannabinoid mechanisms. If a neuronal storm threatens, the endocannabinoids are released to block it. According to Lutz, this protective mechanism plays an important role well beyond epilepsy. "It appears to be quite general," the researcher explains. "If the brain has a problem, it produces endocannabinoids."

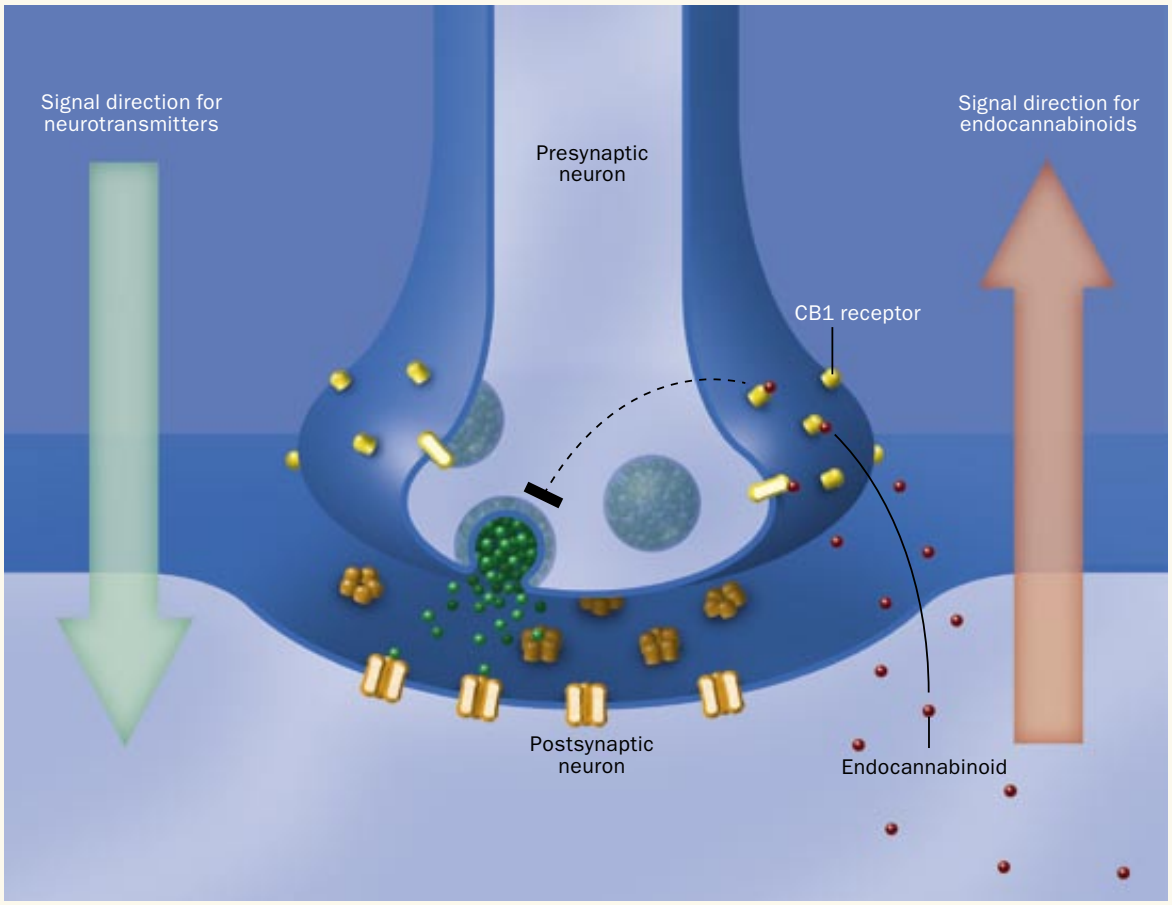
Andrea Giuffrida, a pharmacology professor at the University of Texas at San Antonio, has confirmed this theory working with Parkinson's patients. In Parkinson's disease, neurons in certain brain regions that produce the neurotransmitter dopamine die off. As a result, victims develop severe motor problems. A certain toxin that kills dopamine-producing neurons causes similar symptoms. So Giuffrida injected the toxin into lab mice a few minutes after giving them a synthetic cannabinoid. The cannabinoid prevented the toxin's destructive effects. "The brains of the mice that had been treated with the marijuanalike substance could scarcely be distinguished from those of normal mice," Giuffrida says. He hopes that his work will ultimately lead to compounds that stop the destruction of dopa-

(The Author)

ULRICH KRAFT, a freelance science writer in Berlin, wrote the cover story on burnout in the June/July issue of *Scientific American Mind*.

Retrograde Communication

At a typical synapse, the knob at the end of a neuron secretes neurotransmitters such as glutamate (*green*). These neurotransmitters diffuse across the gap to receptors on a neighboring neuron. The endocannabinoids work in reverse. They are produced in the postsynaptic cell's membrane, then exit and dock at the knob's CB1 receptors. When docking occurs, that tells the presynaptic cell to stop releasing glutamate. The endocannabinoids, acting as neuromodulators, may protect neurons from overarousal.



mine-producing neurons, helping to fight Parkinson's in its early stages.

Zimmer concurs that the endocannabinoids' primary purpose is to help protect the mental organism from stress. He says, "They protect nerve cells not just from overarousal, but also, for example, from the harmful effects of stress hormones such as cortisol." Lutz adds that cannabinoids also "put the body into recovery mode"; muscles slacken, pulse and blood pressure go down, and mental activity is lessened—all signs of relaxation.

Experts are starting to explain various psychological effects as well. They have trained rodents to fear certain stimuli, then retrained them to subsequently learn that the stimuli are no longer a threat, gradually extinguishing the fear. Rodents with missing or blocked CB1 receptors, however, do not lose their fear. The endocannabinoids, it seems, are crucial to diminishing bad feelings, and a faulty system might be a prime contributor to post-traumatic stress syndrome or phobias.

Cravings Killer

That a whole lot of things happen when you flood your brain with THC is old news for marijuana smokers, but the effects have suddenly piqued the interest of the pharmaceutical industry.

The pharmaceutical company Sanofi-Aventis, based in Paris, has developed a new drug

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called Acomplia, which is already in trials. Its active ingredient, rimonabant, blocks CB1 receptors and is thus supposed to help overweight people shed pounds. "Cannabinoids arouse one's appetite, apparently through the reward system," Zimmer explains. Because rimonabant binds to the sites normally used by endocannabinoids, it may be able to stop cravings for food. The principle seems to work, according to results of a company study of 3,000 U.S. and Canadian volunteers, which Sanofi-Aventis released in February. Participants who took the CB1 blocker each day lost more weight than a control group given a placebo. In addition, markers in standard blood tests that indicate a high risk of stroke or heart attack were lower.

How much of the advantage comes from affecting signals among neurons is not clear, however, in Lutz's opinion. He ascribes the positive metabolic effects at least partially to the drug's effect on peripheral organs, which harbor CB1 receptors, too. "In the obese, the endocannabinoid system is overactive in the liver," he says. "Rimonabant seems to restore it to equilibrium."

Of course, eating is not the only activity that triggers the brain's reward system. Many addictive substances do so as well; nicotine prompts the secretion of more dopamine, providing users with satisfied, euphoric feelings. Blocking the endocannabinoid receptors could negate the increased secretion of dopamine, reducing the pleasant feelings that make smokers reach for another cigarette.

Long-Term Concerns

Despite some possible benefits, experts are still wary about tinkering with our natural marijuana network. "The brain is a sensitive system based on inhibitory and excitatory influences, and the endocannabinoids keep this system in balance," Lutz notes.

One fundamental complication is that, like marijuana itself, man-made versions of endocannabinoids do not simply travel only to desired sites. They spread throughout the brain when taken, causing multiple effects, including dizziness, drowsiness, and concentration and thinking problems.

Second, possible side effects related to sustained alteration of the CB1 receptors are unknown and cannot be ruled out. "We have almost no idea what will happen if we inhibit the endogenous cannabinoid system over the long term," Zimmer says of the brain's natural reward mechanisms. His perspective comes from his latest experiments with genetically altered mice. When they were young, the mice did markedly better than their unaltered peers in various learning tests. But at the age of three to five months—the prime of life—the mice without CB1 receptors were learning almost as poorly as normal mice at 18 months old, which is elderly. Studies of the pothead mice revealed they had suffered damage to the hippocampus, the central switchboard for storing memories. The mice that possessed no receptors for their endogenous cannabinoids lost significantly more neurons in the hippocampus than the regular mice did.

> No one anticipated what has proved to be an entirely new communication system in the brain.

This premature cell death, Zimmer believes, could be caused by the loss of the neuroprotective effects of the endocannabinoids. "We must move very carefully to make sure that deliberate medical inhibition of the CB1 receptors does not lead to such damage," he says, adding that appropriate long-term trials must be held before drugs are released for clinical use in human patients. The pharmaceutical industry may have a different point of view, however; companies such as Sanofi-Aventis hope to bring products to the market soon.

Drug sales aside, the unraveling of the endocannabinoid system is exciting neuroscientists. No one anticipated what has proved to be an entirely new communication system in the brain. Further research will outline the complete mechanisms and could provide novel treatments for a wide range of psychiatric conditions and brain illnesses. M

(Further Reading)

- **Endocannabinoid Signaling in the Brain.** R. I. Wilson and R. A. Nicoll in *Science,* Vol. 296, pages 678–682; April 26, 2002.
- **Early Age-Related Cognitive Impairment in Mice Lacking Cannabinoid CB1 Receptors.** A. Bilkei-Gorzo et al. in *Proceedings of the National Academy of Sciences USA,* Vol. 102, No. 43, pages 15670–15675; October 25, 2005.