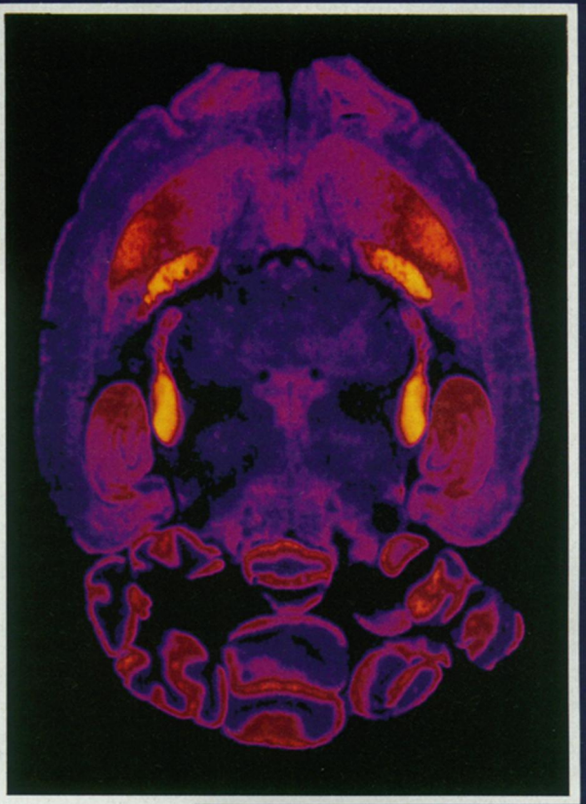
Marijuana and the Brain

Scientists discover the brain's own THC

By KATHY A. FACKELMANN



Herkenham

A very thin slice of a rat's brain is placed on a slide and washed with a radioactive cannabinoid drug. The resulting map shows areas of the brain rich in receptors. In this photo, yellow is the richest area.

William A. Devane was poring over his favorite book, *The Life Divine*, by Indian philosopher Sri Aurobindo, when he came across the Sanskrit word *ananda*, which means bliss. For several years, Devane had been searching for a brain compound that resembles the active ingredient in marijuana. Then and there he decided that if his quest proved successful, he would name the elusive chemical after *ananda*.

Of course, Devane still had to find the compound, a task that involved sorting through thousands of substances active in the brain.

But find it he did. Late in December 1992, Devane and a group of Israeli colleagues at Hebrew University in Jerusalem reported isolating a natural marijuana-like compound in pig brains. Now that he has the marijuana-mimicking, pig-produced chemical, Devane is searching for the same stuff in human brains while working in a cramped laboratory of the National Institute of Mental Health (NIMH) in Bethesda, Md.

The notion that the brain makes its own marijuana fits in with a previous discovery: During the 1970s, neuroscientists found that nerve cells manufacture compounds that resemble opium, an addictive drug obtained from the juice of the seeds of the poppy plant.

This finding spurred an intensive effort to understand the brain's natural opiate. Also in December 1992, two separate teams reported that they had mapped the structure of one of the opiate receptors, a protein on the nerve cell surface that recognizes and binds opiates, thus allowing these drugs to produce their mind-altering effects.

Taken together, the reports raise many questions about why the healthy brain produces chemicals that resemble marijuana and opium. Many scientists speculate that such internal compounds help humans cope with stress and pain. The findings may help neuroscientists figure out how these brain-made substances work at the molecular level. Ultimately that knowledge will help drug designers develop better painkillers and stress busters.

Marijuana — also known as grass, pot, Mary Jane, and a host of other names — refers to the dried leaves and flowers of *Cannabis sativa*, a plant widely — and illegally — used in the United States as a recreational drug. Users typically roll the leaves into a paper wrapper and smoke the resulting marijuana cigarette. In small to moderate doses, delta-9-tetrahydrocannabinol (THC), the plant's active ingredient, produces feelings of well-being and euphoria. In large doses, the drug can cause paranoia, hallucinations, and dizziness.

But recreation isn't the only reason people smoke marijuana. Many people suffering from glaucoma turn to illicitly obtained marijuana to help restore their vision. The Drug Enforcement Administration still considers marijuana a Schedule 1 drug, however — one that has no accepted medical use. That may change. Joycelyn Elders, the Arkansas state health official who has been tapped as President Clinton's Surgeon General, has gone on record supporting the use of marijuana in the treatment of diseases such as glaucoma.

Synthetic versions of THC are available with a doctor's prescription. In 1985, a lab-made THC received Food and Drug Administration (FDA) approval as an anti-nausea agent for cancer patients (SN: 6/15/85, p.377). And in December 1992, FDA approved the same drug to combat the weight loss that afflicts some people with AIDS. Physicians can also prescribe the synthetic THC for treatment of glaucoma, even though FDA has not specifically approved marketing the drug for that use.

Devane's search for "bliss" began in the 1980s, when he was completing his doctoral studies in pharmacology at the St. Louis (Mo.) University School of Medicine. In 1988, Devane, who had been working with cannabinoid researcher Allyn C. Howlett, discovered that the membranes of nerve cells contain protein receptors that bind THC. Once securely in place, THC kicks off a series of cellular reactions that ultimately lead to the "high" that users experience when they smoke a marijuana cigarette.

The very existence of such a receptor implied that the human brain manufactures a marijuana-like substance: It seemed unlikely that humans had a specialized receptor just waiting for the plant-derived THC to show up. Thus, the 1988 discovery had laboratories all over the world scouting for a THC look-alike.

Doctorate in hand, Devane left St. Louis for Jerusalem to pursue his search by working with Raphael Mechoulam, the Hebrew University chemist who had determined THC's structure.

Before Devane, Mechoulam, and their colleagues could begin looking for the body's version of THC, they had to design a radioactive THC-like drug, or marker, whose location could be traced during brain cell studies. They fashioned such a drug, then mixed it with THC receptors; they found that the marker locked onto its target.

The Israeli team needed a reliable source of brain cells. They couldn't get human brains, so Devane turned to a local butcher shop, where he bought pig brains. After grinding the brains up in a blender, the researchers had to sort through and separate thousands of brain chemicals. They tested each one to see if it would displace the radioactive THC from the receptor.

Devane calls that search a little like looking for a needle in a haystack. But eventually the team's hard work paid off: They discovered a substance that fit neatly into the THC receptor.

The researchers labored for two more years to get enough of the purified compound — a drop of clear, oily fluid — to examine in detail. Using a technique called mass spectrometry, they determined the structure of the substance. Devane, of course, had no trouble coming up with a name, anandamide.

Anandamide is derived from arachidonic acid, a 20-carbon carboxylic acid that is the starting point for a cascade of complex biochemical reactions. One branch of that cascade leads to the production of the leukotrienes, key substances in the inflammation process. Another branch leads to substances known as prostaglandins, which play a role in mediating pain. Devane believes another, as yet uncharted branch of this cascade leads to anandamide.

The Hebrew University scientists weren't through with anandamide just yet. They had shown that the new compound docked with the THC receptor, but they still had to demonstrate that anandamide stimulates the receptor and leads to effects similar to those produced by THC. So Devane and his Israeli colleagues turned to a classic experiment with mice.

They began by isolating sections of the mouse vas deferens, the muscular duct that carries sperm from the testes to the urethra. They knew that the vas deferens contracts when jolted by an electric shock and that THC inhibits this so-called twitch response. The investigators discovered that anandamide works like THC, preventing the vas deferens from contracting after electrical stimulation.

Their finding indicates that anandamide behaves like THC, at least in this mouse model. The Israeli team published their findings in the Dec. 18 SCIENCE.

The saga of anandamide is far from over. When Devane left Hebrew University last year, he took his interest in this marijuana-like drug with him to NIMH. In Building 36 on the grounds of the National Institutes of Health, Devane and his NIMH colleagues continue to gather data on this intriguing chemical.

Indeed, Chris Felder and Eileen Briley, two of Devane's co-workers, have collected more powerful evidence that anandamide functions like the body's own THC.

Felder and Briley wanted to construct a laboratory model of the way the active ingredient in pot interacts with a cell. To do that, they inserted the human gene that codes for the THC receptor into hamster cells. When the researchers bathed the doctored cells with THC, they measured the expected drop in the cell's production of cyclic AMP, a key chemical involved in many cellular reactions.

Next, Felder and Briley took a petri dish filled with genetically altered hamster cells and poured in a purified form of anandamide. Again, they measured a decline in cyclic AMP. Unaltered cells treated with anandamide showed no such drop.

Anandamide didn't produce as big a drop in cyclic AMP as THC did. This suggests that the natural marijuana-like substance produced by human brains may be weaker than the plant-derived THC. "It is not quite as potent as delta-9, but it's close," says Felder, who notes that their research has not yet been published.

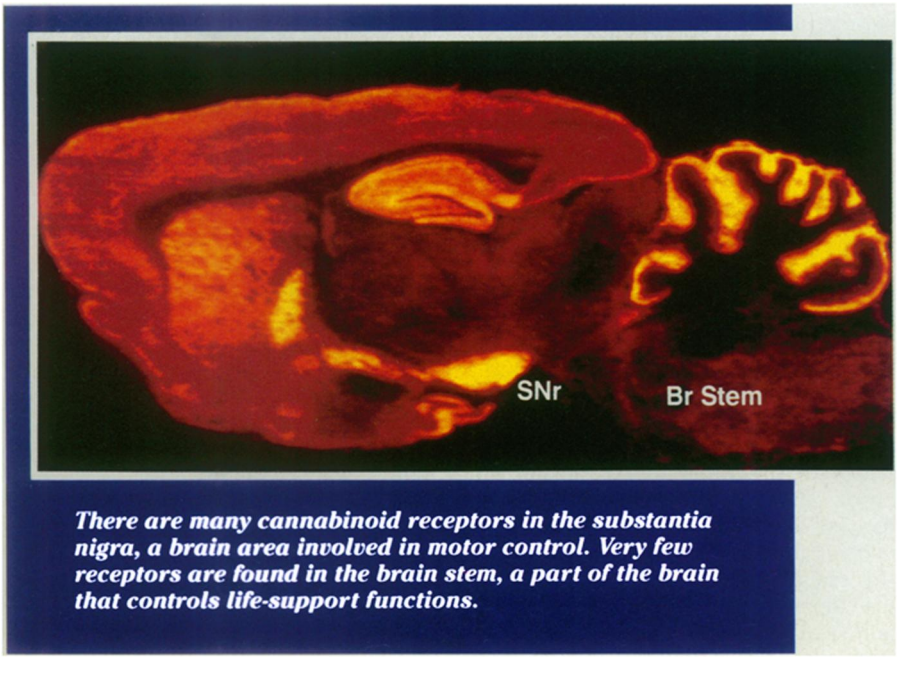
Will purified, concentrated doses of anandamide produce mind-altering effects in humans? Devane and Felder don't know yet, but they are hoping to test the compound in humans shortly.

In the smaller doses that occur naturally in the body, anandamide may be involved in the regulation of mood, memory, pain, movement, and other activities, Devane says.

The brain's reaction to marijuana may help explain the role of anandamide, says Michael J. Brownstein, chief of the NIMH Laboratory of Cell Biology. He notes that dogs given large doses of THC will stumble as though they were drunk. This observation suggests that a defect in anandamide or its receptor may cause certain diseases characterized by loss of motor control.

For example, some scientists speculate that the natural marijuana-like substance may play a role in Huntington's chorea, a progressive hereditary disease that interferes with muscular control. There's no proof that anandamide is connected to Huntington's disease, cautions Miles A. Herkenham, an NIMH scientist. However, Herkenham's preliminary data suggest that people with Huntington's lose lots of THC receptors early in the disease process, even before symptoms start to surface. Herkenham's previous research (SN: 11/26/88, p.350) produced a map of the THC receptors in the human brain.

Others wonder if anandamide plays a role in eating disorders such as anorexia and excessive eating. Regular users of marijuana say that the drug leads to a feeling known as "the munchies." Scientists know that THC can, in fact, trigger a glucose craving. Such evidence suggests that anandamide is involved in appetite control, Brownstein says.



Herkenham

There are many cannabinoid receptors in the substantia nigra, a brain area involved in motor control. Very few receptors are found in the brain stem, a part of the brain that controls life-support functions.

The search for anandamide began with the discovery of the THC receptor. The flip side of that story is being played out in the related field of opiate research.

Several decades ago, neuroscientists identified endorphins and enkephalins,

Continued on p.94

Books

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Dreams of a Final Theory: The Search for the Fundamental Laws of Nature – Steven Weinberg. From a Nobel laureate and author of *The First Three Minutes* comes an updated look at where theorists stand in their quest for a "Grand Unification Theory": the answer to all physical science. Weinberg defines the concept of a final theory and expounds on the quest for it – past, present, future – and ponders the potential effects on mankind of finding an answer. Finally, he devotes a chapter to the pros and cons of the $8 billion Superconducting Super Collider, which some people feel will be the necessary link to a final theory. In this book, the narrative, background, and author's case for his own theories and conclusions are intermingled in a manner that the general reader can comprehend and enjoy. Extensive endnotes explain certain aspects of the book at a higher level. Pantheon, 1992, 334 p., hardcover, $25.00.

Eight Little Piggies: Reflections in Natural History – Stephen Jay Gould. A collection of 31 essays from Gould's regular feature in NATURAL HISTORY magazine comprise Gould's sixth volume in a continuing series. Specific topics detail the importance of preserving the Mount Graham red squirrel and the effect of the extinction of land snails that inhabited the island of Moorea on a man who devoted his life to studying them. The title refers to the discovery of eight digits on each hand of the first land vertebrates, which defeated the belief that five is better. Gould's fans certainly will enjoy his latest opus of reflections. Norton, 1993, 479 p., illus., hardcover, $22.95.

The Enigma of Suicide – George Howe Colt. Between 1 and 2 percent of Americans die by suicide, according to Colt. Determined to dispel the cultural taboo surrounding the subject, he embarks on a comprehensive exploration of suicide's social, cultural, and legal history; suicide-related research, ranging from genetics to psychoanalytic theory to the effects of television; preventive efforts and support resources for bereaved relatives; "right-to-die" issues; and what suicide may mean in the minds of people who decide to kill themselves. This compassionate account is based on hundreds of interviews with survivors of suicide attempts, friends and relatives struggling to cope with suicide losses, and professionals who work with suicidal individuals. Originally published in hardcover in 1991. Touchstone Bks, 1992, 575 p., paperback, $14.00.

Life, Death, and in Between: Tales of Clinical Neurology – Harold L. Klawans. A neurologist recounts life-and-death experiences and medical dilemmas faced by ordinary people in this fascinating look at decisions and predicaments we hope never to face. Klawans outlines his often frustrating role as consultant and researcher and discusses ethical and philosophical predicaments such as the removal of life support, the importance of death at home, and experimental drugs and treatments. People profiled include a paralysis victim whom Klawans was able to diagnose but on whom no surgeon was willing to undertake pioneering surgery. Klawans had to wait until his patient died to do an autopsy and prove himself right. He published his findings, and now that corrective surgery is commonplace. Paragon Hse., 1992, 270 p., hardcover, $21.95.

Reversing Memory Loss: Proven Methods for Regaining, Strengthening, and Preserving Your Memory – Vernon H. Mark with Jeffrey P. Mark. The authors, a former chief of neurosurgery at Boston City Hospital and a coauthor of *Brain Power,* outline new tests, diagnoses, and treatments for memory loss. They emphasize that as many as 30 percent of the cases diagnosed as Alzheimer's disease may instead trace to other, treatable problems. They also cite depression, stress, substance abuse, and overmedication as increasingly common causes of memory loss and discuss cases of brain damage or disease that can be helped, if not completely reversed. Originally published in hardcover in 1992. HM, 1992, 244 p., paperback, $9.95.

Continued from p.89

opium-like compounds manufactured by the human brain. At that time, researchers also had evidence that opiate receptors existed. Yet their search for the structure of such receptors remained unsuccessful until late last year, when peptide chemist Christopher J. Evans of the University of California, Los Angeles, and his colleagues finally obtained a detailed picture of one type of opiate receptor. They published their finding in the Dec. 18 SCIENCE.

The endorphins and enkephalins are similar to opium, heroin, and morphine, drugs derived from the seeds of the poppy plant *Papaver somniferum.* Evans and his co-workers have identified and described the messenger RNA that carries the genetic blueprint for one type of opiate receptor from the DNA of a cell's nucleus to the receptor's production site.

Why did it take so long? Evans says the messenger RNA for opiate receptors is very rare and difficult to isolate. But once they had the messenger RNA, the team could determine the amino acids that make up the receptor.

After years of searching for one of these elusive receptors, a second team has also characterized an opiate receptor – almost certainly the same one as Evans' group. In the Dec. 15 PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES, Brigitte L. Kieffer of the Ecole Supérieure de Biotechnologie in Strasbourg, France, and her co-workers describe an opiate receptor that looks remarkably similar to the one the U.S. team nabbed.

The opiate receptor and the THC receptor belong to a family of proteins that do their work via molecules called G-proteins. Evans says such receptors work this way: An opiate or THC-like drug binds with the receptor on the outer surface of the cell. Once activated, the receptor acts on G-proteins inside the cell, a process that leads to a cascade of biochemical reactions – and a feeling of euphoria.

The U.S. and French investigators identified the delta opiate receptor, a type of receptor that binds with enkephalins. In the future, researchers hope to find several other types of opiate receptors, a goal that should be easier now that a map of the delta receptor exists. Evans believes that a handful of genes probably direct the production of a host of opiate receptors, including this one.

Neuroscientist Gavril W. Pasternak of the Memorial Sloan-Kettering Cancer Center in New York City predicts that the mapping of an opiate receptor will "revolutionize" the field of opiate research. Knowing the structure of this receptor (and others, once they are mapped), drug designers can begin to fashion new opiate compounds, perhaps ones that fulfill the age-old promise of relief from pain without ill effects.

How is it that the brain evolved to manufacture compounds that resemble drugs of abuse?

Some scientists speculate that as organisms evolved from single-celled creatures to complex ones, they needed a system to regulate a welter of interrelated physiological functions. Thus, humans and other creatures developed neurotransmitters, chemical messengers that allow nerve cells to communicate with one another in the brain and with other cells in the body.

Like anandamide, the endorphins and enkephalins play a role in the healthy brain and are probably involved in immune function, motor control, and pain relief, Evans speculates.

Such brain chemicals also play a part in an organism's response to danger, a throwback to the time when immediate pain relief meant animals could flee from an attacker without delay. Most modern humans don't have to worry much about tiger attacks, but stress remains ubiquitous. As neuroscientists learn more about anandamide, the endorphins, and their protein receptors, they will begin to compile a much better picture of the way these feel-good chemicals influence human behavior. □