that contain an estimated 116 million people—almost a quarter of the population of sub-Saharan Africa.

The paper "cuts against much of the ethos of the conservation movement that wants to preserve absolutely pristine environments," May says. "I share that feeling, but there has to be much more work on determining minimal ecological structure: How much of the original habitat do you have to keep to enable particular plants and animals to coexist with humans?" Tom Lovejoy, a tropical biologist at the Smithsonian Institution and a consultant with the World Bank, says the work lends support to "mixed use" projects like the Mesoamerica biological corridor in Central America. The project aims to include strict protected areas as well as bird-friendly coffee plantations and regions in which a hydroelectric project will pay owners of the watershed as an incentive to preserve the forest.

But mixed-use strategies get mixed reviews. In some regions, Fonseca says, "the only way you're going to make sure anything is left is by having secure borders and protecting what you have." He says the study highlights the fact that if African biodiversity is to survive, "at some point we have to bite the bullet and make some very strong choices, even if those are costly and difficult both economically and socially," such as creating well-protected parks and compensating local residents.

The study should help guide some of those choices, Balmford says. Fonseca agrees. "We can't make these decisions unless we know where the species and people are," he says. "They've done that analysis in an extremely comprehensive way."

–GRETCHEN VOGEL

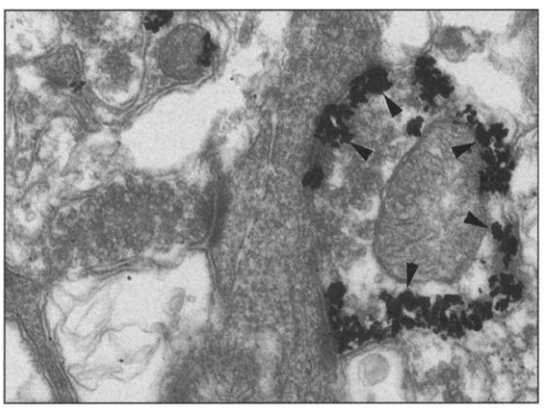
NEUROBIOLOGY

How Cannabinoids Work in the Brain

Marijuana may provide a euphoric high, but it can also boggle one's memory. The impairment is so pronounced in laboratory rats under its influence that they behave in some learning tasks as if a key memory area in their brains, the hippocampus, had been removed entirely. Now, the story takes an intriguing twist: Researchers have discovered that the "endogenous cannabinoids," marijuana-like chemicals made by our brain whose function has long been a mystery, play key roles in a process that may be central to the laying down of memory, among other things.

In reports this week in *Nature* and *Neuron*, three independent research teams—from the University of California, San Francisco (UCSF); Kanazawa University School of Medicine in Japan; and Harvard Medical School in Boston—have shown that cannabinoids are dispatched by some brain neurons to fine-tune the signals they receive. The cannabinoids accomplish this by turning down the activity of the neurons doing the signaling. One form of the process, known as depolarization-induced suppression of inhibition (DSI), occurs in the hippocampus, a brain area involved in memory, and in the cerebellum, which coordinates movements.

The discovery unites two previously unlinked research tracks. It offers "the first concrete example of physiological function" for the endogenous cannabinoids, says neuroscientist Leslie Iversen of the University of Oxford, U.K. And it finally reveals the identity of the molecule responsible for DSI; researchers had been searching for this so-called retrograde messenger for nearly 10 years.



Receptive. Antibodies to the cannabinoid receptor (black dots) are clustered in the membrane of an inhibitory neuron in a human hippocampus.

CREDIT: I. KATONA *ET AL., NEUROSCIENCE* 100, 797 (2000)

"This is extremely exciting," says neuroscientist Brad Alger of the University of Maryland Medical School in Baltimore, whose team discovered hippocampal DSI in the early 1990s. Now researchers can manipulate the cannabinoid messengers, he says, to "dissect out the roles of DSI in brain function and behavior." Alger believes it may prime individual neurons in the hippocampus for long-term potentiation (LTP), the synapse strengthening thought to be central to learning and memory. The discovery also has generated new insights into how marijuana intoxicates the brain.

None of the groups set out to solve the cannabinoid mystery. All were searching for the elusive signaling molecule in DSI. Two years ago, Rachel Wilson, a graduate student with Roger Nicoll at UCSF, took up the hunt. In slices of rat hippocampus, she showed that neurons produce the messenger in response to rising internal calcium levels and that, in contrast to most neurotransmitters, the messenger is not packaged in vesicles for release.

To Jeff Isaacson, a former student with Nicoll who was visiting the lab, those characteristics rang a bell: They're shared by the endogenous cannabinoids. On his suggestion, Wilson treated the brain slices with a chemical that blocks the function of cannabinoid receptors. It blocked DSI. "That experiment alone was the story," says Nicoll. Wilson confirmed with more experiments that a cannabinoid is the messenger, and she presented her work last November at the annual meeting of the Society for Neuroscience in Miami; her paper appears in this week's *Nature*.

During that same time, Takako Ohno-Shosaku, working with Masanobu Kano at Kanazawa University, was on a parallel course. Having taken her clue from a 1997 paper from Daniele Piomelli's team at UC Irvine, which showed that activated hippocampal neurons release endogenous cannabinoids, Ohno-Shosaku also found that a cannabinoid blocker prevents DSI in cultured hippocampal neurons. Her results are in this week's *Neuron*.

Neuroscientist Tamás Freund of the Hungarian Academy of Sciences in Budapest says his team had a clue that cannabinoids play a role in DSI: The researchers showed in 1999 that cannabinoid receptors in the hippocampus are located exclusively on the inhibitory neurons that receive the retrograde signal. "The amazing selective localization of the receptors made them an excellent candidate to mediate DSI," says Freund.

Meanwhile, Wade Regehr and graduate student Anatol Kreitzer at Harvard Medical School found that excitatory signals can also be inhibited, in a process similar to DSI that they called DSE. Working in slices of cerebellum, Kreitzer found that increased calcium levels trigger neurons to release the messenger that initiates DSE, but he was not able to identify it. After talking with Wilson at her poster presentation at the neuroscience meeting, he tried blocking cannabinoid signals. As he and Regehr report in this week's *Neuron*, this wiped out DSE, implicating cannabinoids in turning down excitatory as well as inhibitory inputs. The discovery that "excitatory synapses can do it, too," is important, says Stanford University neuroscientist Dan Madison, because "that makes it more widely useful" to the brain.

"I'd be really surprised," Madison adds, if DSI and DSE aren't found in other places in the brain. His hunch may soon be confirmed. Freund's group has found cannabinoid receptors in the amygdala, an area involved in emotional memory, on the same class of inhibitory neurons as those on which it is found in the hippocampus, so DSI may occur there. And last year, Yuri Zilberter of the Karolinska Institute, Sweden, reported a DSI-like phenomenon in the cerebral cortex of rats. Now,

Alger says, researchers can use cannabinoid-receptor blockers or mice lacking cannabinoid receptors to see whether cannabinoid-mediated DSI occurs in these brain areas and to pin down its roles in brain function.

The studies also shed light on how marijuana affects brain functions such as memory, says Alger. "For years people thought that cannabinoids disrupt the development of LTP," he says, but now it appears that endogenous cannabinoid release may instead enhance it, by triggering DSI. But whereas the normal effects of DSI and DSE are limited to just the neurons in the vicinity of those releasing the cannabinoid and last only tens of seconds, marijuana use exposes the entire brain to high levels of marijuana's active ingredient, tetrahydrocannabinol (THC), for much longer. That would "swamp the whole system," says Irvine's Piomelli.

And that may explain findings such as those reported last December in the *Journal of Neuroscience* by Sam Deadwyler's team at Wake Forest University School of Medicine in Winston-Salem, North Carolina, showing that THC-treated rats behave on some memory tests as if they had no hippocampus. THC flooding the brain would eliminate the local activity patterns set up by DSE and DSI, just as spilling a bottle of ink across a page obliterates any words written there.

–MARCIA BARINAGA

MARINE MAMMALOGY

River Dolphins Add Branches to Family Tree

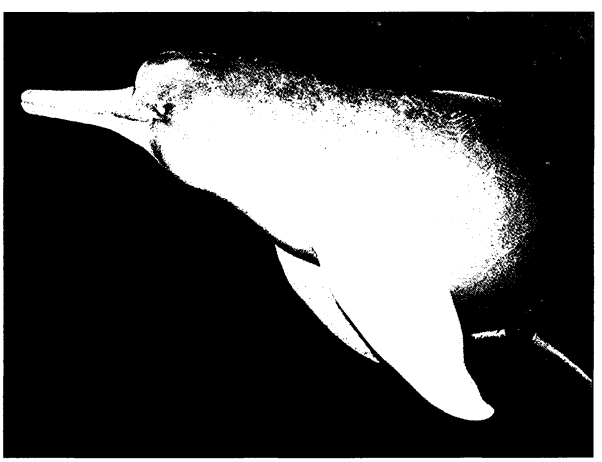
YOKOHAMA—Scientists who study marine mammals have long puzzled over where to place four species of river dolphins on the family tree. Similar in appearance, the Ganges, Yangtze, Amazon, and La Plata dolphins were thought to be more closely related to each other than to their whale cousins. But new data from a genetic analysis suggest that the species diverged at different times. One of the species may have diverged before beaked whales, whereas most dolphins did not appear until much later.

Norihiro Okada, a molecular biologist at the Tokyo Institute of Technology, and colleagues presented results here* based on a technique that uses unique repetitive bits of DNA, called short interspersed elements (SINEs), that are inserted randomly throughout the genome. Okada says the probability of identical but independent insertions at the same location in unrelated species is vanishingly small, as is the possibility of an insertion being precisely deleted later in evolutionary time. "It's the golden method" for molecular studies of evolution, says Hans Thewissen, a paleontologist at Northeastern Ohio Universities College of Medicine in Rootstown.

Okada and his colleagues gathered DNA samples from 14 cetacean species and identified 25 new SINEs, from which they constructed a relative timeline of whale, dolphin, and porpoise divergence. One significant conclusion was that the molecular analysis shows a clear separation between toothed whales, or Odontoceti, and baleen whales, or Mysticeti. Although this is the traditional morphological division, previous molecular analyses had been divided on the issue.

Based on his analysis, Okada believes that toothed marine animals diverged in the following order: sperm whales, Ganges river dolphin, and beaked whales, followed by the remaining freshwater and marine dolphins. No SINEs were found that could be used to resolve the relationships between those remaining freshwater and marine dolphins, although some SINEs indicate a sister relationship between the two South American river dolphins (Amazon and La Plata), and other SINEs clearly group together the remaining marine dolphins. Despite these gaps, Okada says that "the analysis still clearly shows that river dolphins are paraphyletic."

The new analysis supports a growing number of morphological studies, says Christian de Muizon, a paleontologist at the National Museum of Natural History in Paris, "so I was quite happy to see these results." And Ulfur Arnason, a molecular phylogeneticist at Lund University, Sweden, adds that Okada's results are also consistent with a growing number of molecular studies. Both agree that the results strengthen the case for



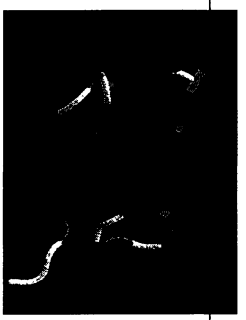
CREDIT: (DOLPHIN) VARIN–VISAGE/JACANA/PHOTO RESEARCHERS

Intruder. The Ganges river dolphin may fit between sperm and beaked whales on the evolutionary tree.

* Evolution and Adaptation of Marine Mammals, 12 March, Tokyo Institute of Technology, Nagatsuta campus.

ScienceScope

Courting a Consortium A former pharmaceutical executive is trying to shake up the proteomics world. Alan Williamson, a retired Merck & Co. official, is pushing an ambitious plan to have companies solve the structures and functions of 200 human proteins a year—then give away what they learn.



It might sound implausible. But the project has already won a pledge of support from The Wellcome Trust, a British charity. Williamson also claims that "nine or 10" firms are thinking of contributing $3 million each to the consortium, which he hopes will begin work this year. He hopes to seal these commitments with a business plan in the next few weeks.

Williamson has pulled off a similar coup in the past. He was instrumental in launching the SNP Consortium, which has made public more than 850,000 single-nucleotide polymorphisms (SNPs), the genetic variations that may be used to study diseases (*Science*, 16 April 1999, p. 406). The new proteomics group, he argues, could play a similar role in jump-starting drug development by sharing basic knowledge.

You've Got Mail President George W. Bush and Secretary of Health and Human Services Tommy Thompson received yet another letter this week urging them to allow the federal government to fund research on embryonic stem cells (*Science*, 1 September 2000, p. 1442). Antiabortion groups and some lawmakers are opposing the plan, because it involves extracting cells from embryos. But 112 university presidents have now joined 95 members of Congress and 80 Nobel laureates in urging the Administration not to backtrack.

Meanwhile, eight groups—including the American Society of Cell Biology, the Juvenile Diabetes Research Foundation International, and Harvard University—have hired some lobbying muscle to fight for stem cells. Vicki Hart, a consultant and aide to former Senator Bob Dole, will help the new Coalition for the Advancement of Medical Research make its case.

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