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In the summer of 1999 I was finishing my 13th year as managing editor of Synapse, the UC San Francisco weekly. The paper was staffed and produced mainly by medical students, with grad students and students from the schools of Pharmacy, Nursing and Dentistry also taking part.With the students gone in July and August, Synapse appeared monthly and I did some of the writing.

I used vacation time in June '99 to attend the International Cannabinoid Research Society meeting in Acapulco, and the meeting provided a perfect hook for a Synapse story! UCSF pharmacologist Lester Bornheim presented a paper on cannabidiol —giving me a local angle and a platform to start preaching the gospel of CBD back in the US of A.

The following piece ran in the July 1999 issue of Synapse, accompanied by photos of Bornheim in his lab at UC; Bornheim conferring with Geoffrey Guy at the ICRS meeting; and Aidan Hampson of the National Institutes of Health, who had established that CBD has neuroprotectant properties... . I'm kicking myself for operating with the mentality of a leafleter, not thinking beyond getting a good graphic or two for use in a black-and-white tabloid... I coulda been a collector! —*FG*


UCSF synapse July, 1999

Commentary
Pressure On Dental Students— How to Reduce it?
By Jean Creasey

Rites of Summer

Third-year medical students practiced drawing blood on dummies prior to practicing on whether (themselves). Soon they'll be on the wards, drawing blood from patients.

Cuts at Mount Zion Weighed; Merger Faces Criticism

THC's uncelebrated cousin
Bornheim Studying Effects of CBD, A Nonpsychoactive Cannabinoid
By Fred Gardner

Cannabinoid Metabolism

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When the International Cannabinoid Research Society held its annual meeting last month in Acapulco, UCSF's Lester Bornheim, IPhD, had the pharmaceutical entrepreneur Geoffrey W. Guy taking careful notes. Since the mid-1980s Bornheim, a researcher in the Department of Cellular and Molecular Pharmacology, has been studying the metabolism of eannabidiol (CBD). This compound in the cannabis plant, unlike THC, its celebrated relative, does not result in a "high" when inhaled or ingested.

THC is frequently described as the "active ingredient" in cannabis, but this is a misnomer. THC is the predominant compound in cannabis plants that have been bred for psychoactive potency —i.e.. marijuana. CBD is the predominant compound in cannabis plants that have been bred for fiber i.e.. hemp. CBD has shown potential as an anticonvulsant —-an antiepileptic in humans — in studies dating back 20 years. It also has antioxidant and neuroprotective effects. Aidan Hampson, PhD, of the National Institute ol Mental Health (formerly a postdoe in Bornhcim's lab) has shown that rats treated with CBD incur less damage when they suffer strokes.

How CBD might function as an anticonulsant is unknown. A high-CBD plant extract will be tested as a treatment for epilepsy in clinical trials being planned by Robert Gorter, associate clinical professor of medicine at UCSF. Bornhcim has agreed to consult in the trials, which will be conducted in Europe.

But any drug company seeking to exploit the therapeutic potential of CBD will have to deal with a significant side-effect, discovered by Bornheim: in the liver, CBD inactivates cytochrome p450 enzymes (which are involved in metabolizing most clinically useful drugs).

Cannabinoid Metabolism

When cannabinoids are inhaled, they enter capillaries in the lungs and pass into the general circulation through the pulmonary veins. The circulation can carry intact cannabinoids directly to the brain, or to the liver to be metabolized. Derivatives formed in the liver —metabolites —can also enter the brain through blood circulation. When cannabinoids are ingested orally, they are absorbed in the small intestine and then carried directly to the liver, where ihey arc metabolized. These different modes of administration could yield different pharmacological profiles, with more metabolites formed as a result of oral ingestion.

Bornheim started studying drug metabolism in 1977 as a grad student at the University of Utah He came to UCSF in 1982 as a postdoc to study the P450 system. In 1987, as a research pharmacologist, he awarded a NIDA gram to study the effects of cannabinoids on P450. That grant, which has been renewed every four years, funds Bornheim's salary and the salaries ol a postdoc or a staff research assistant, as well as their experiments and related costs.

P450 is a "super family" of enzymes that metabolizes most of the drugs we take. "Virtually every drug that has been invented 0r will be invented is a substrate for P450." says Bornheim. "It's a very unusual enzyme. Almost all other enzymes are designed to fit a single substrate and carry out a single chemical process resulting in a single product." P450 appears to be an almost universal breakdown mechanism.There are more than a dozen significant P450s in the liver that, according to Bornheim, "metabolize different drugs with varying affinities and turn them into different products. P45os not only metabolizc all the exogogenous drugs we take but they metabolize many endogenous compounds."

.At the 1999 ICRS meeting in Acapulco, Bornheim reported on experiments conducted with postdoc Michael Reid, PhD, in which pre-treatment of mice with CBD markedly increased brain levels of subsequently administered cocaine or phencyclidine (PCP). These studies were an extension of previous work demonstrating that CBD pre-treatment increased brain levels of THC and its metabolites. When cocaine levels in the brain were found to be elevated by CBD, parallel increases in the blood were also detected. But when THC levels in brain are elevated by CBD, blood levels are unchanged. Understanding this paradoxical effect is one of Bornheim's research goals.

CBD does not react with the cannabinoid receptors. Bornheim is attempting to determine whether it exerts its effects by altering transport of drugs into or out of the brain, or by altering plasma protein binding. Bornheim also intends to test the effect of CBD on brain levels of therapeutic drugs used to treat brain tumors —drugs which are difficult to introduce into the brain. To date he has determined that pre-treatment with CBD does not, increase brain levels of subsequently administered methotrexate or sfluorouracil (anti-neoplastic agents used in cancer chemotherapy).

Morphine is an obvious candidate for testing. As Bornheim puts "The holy grail is being able to use narcotics without getting addicted. If you can increase the amount of morphine in the brain [by CBD pretreatment] you can give less, which may reduce some side effects." At the end of Bornheim's ICRS talk, many hands were raised to ask if he'd determined whether pre-treatment with CBD increased brain levels of various compounds. "They were all valuable questions," he says, "but I can only deal with one drug at a time."


LESTER BORNHEIM IN HIS LAB AT UCSF.

Bornheim's talk was of special interest to Guy, whose company, G.W. Pharmaceuticals, is developing a laser-driven drug delivery system that will "nebulize" cannabinoid extracts. If CBD has a potentiating effect, lower doses of THC and other components may suffice, based on a sequenced delivery schedule. "It's nice that somebody is out there looking at what you're doing for clinical significance and designing studies to test it," commented Bornheim after he and Guy met in Acapulco.

The Decade of the Cannabinoids

The ICRS was organized in 1990 by scientists who had been following each others' work in the literature and conferring informally for years. The first meeting, held in Crete in 1990, drew 45 participants and was chaired by Rik Musty, a professor of psychology at the University of Vermont. Originally the "C" in ICRS stood for "Cannabis," but in 1995, because so few members were actually conducting research with the plant, a vote was taken to change the C-word to "Cannabinoid," which refers to compounds synthesized in the lab or produced by the body, as well as extracted from the plant. The body's own cannabinoids are said to be "endogenous," and are now being called "endocannabinoids" —just as the body's own chemicals with morphine-like effects were dubbed "endorphins."

Bornheim observes, "The whole [cannabinoid] field is very similar to the opiates. We've known for years that this plant had a marked effect in man. It wasn't until we could get a sufficiently labeled, highly radioactive version of the compound that we could detect that there were receptors in brain."

The first plant cannabinoids were identified in the early 1940s by a University of Illinois chemist named Roger Adams. He isolated cannabidiol, cannabinol, and a crude form of tetrahydrocannabinol. To date more than 60 cannabinoids have been found, most of them inactive when inhaled or ingested into the body. The cannabis plant also contains hundreds of chemical substances that are not unique to it.

In 1964 the precise structure of delta-9 THC was described in a paper by Raphael Mechoulam and Y. Gaoni of the Weizmann Institute of Science in Rehovoth, Israel. This triggered a long search in Mechoulam's lab and elsewhere for synthetics that would have the therapeutic effects of THC without the psychoactivity. In 1974 Eli Lilly produced a synthetic version of THC that has been marketed in England and elsewhere as Nabilone. (A drug was determined to be a cannabinoid if it reduced pain, body temperature, spontaneous activity and motor control.)

THC is reportedly a weak partial agonist that exerts a fleeting effect. The first synthetic that would bind strongly enough to be used as a research tool was Pfizer's CP55-940. Sterling Winthrop subsequently developed another class of cannabinoid agonists, the aminoalkylindoles, typified by WIN 55,212--22. The existence of cannabinoid receptors in brain (CB1 receptors) was established in 1988 by binding studies conducted by Alynn Howlett and William Devane at the University of Washington in St. Louis. The CB1 receptor was cloned in 1990 by Lisa Matsuda and colleagues at the National Institutes of Health.CB1 receptors are far more prevalent than opioid receptors in brain. They are concentrated in the cerebellum and the basal ganglia (regions responsible for motor control, which may explain why marijuana reportedly eases muscle spasticity), in the hippocampus (storage of short-term memory), and the limbic system (emotional control). In 1992, Devane and Mechoulam, working together at Hebrew University, identified an endogenous cannabinoid —arachidonoylethanolamide, or AEA, which they named "anandamide" after the Sanskrit word for "bliss."

A second endogenous agonist, 2-arachidonoyl glycerol-(2-AG), has been found in the brain at concentrations 170 times greater than anandimide. It now appears to be responsible for most CB 1-receptor-mediated effects. And some researchers feel that, because AEA and 2-AG have relatively weak affinities for the cannabinoid receptor, the most important endogenous agonist has yet to be discovered.

In 1993 Munro et al found a second cannabinoid receptor (CB2) in spleen cells, white blood cells, and other tissues associated with the immune system. Both cannabinoid receptors are seven-transmembrane domain proteins coupled to G-proteins inside the cell. The first CBI antagonist, 5R141716A, was synthesized by Rinaldi-Carmona of Sanofi labs in 1994. Eli Lilly and Pfizer have also developed cannabinoid antagonists for research purposes. Sanofi's 5R141716A is currently in phase II clinical trials in Europe as an antipsychotic.

Antagonists selective for the CB2 receptor have also been discovered, including SR 144528 (Sanofi Recherche) and AM-281 (Makriyannis and Pertwee).

Some Meeting Highlights

At the 1999 ICRS meeting, several significant advances were reported. Diana L. Cichewicz and Sandra Welch of Virginia Commonwealth University described a study in which mice were given low doses of THC and morphine in combination for

continued on next page

Lester Bornheim and geoffrey guy conferred ater after Bornheim presesnted his paper at the International Cannabinoid Research Society meeting in Acapulco June 21. Guy has been licensed by the UK Home Office to produce cannabis plant extracts for use in clinical trials.

eight days. Analgesia was achieved without side-effects, suggesting a method to prevent morphine tolerance. The investigators called for clinical trials in which cancer patients with chronic pain are treated with a THC-morphine combination.

• Walter Fratta and co-workers at the University of Cagliari reported in a poster that mice will self-administer cannabinoid agonists (the WIN compound and CP55940) as well as opioid agonists (although they abjure pure THC). Pretreatment with Sanofi's CBI antagonist completely prevented self-administration of both agonists, suggesting that cannabinoid reinforcing effects are specifically mediated through CB 1 receptors. Pretreatment with naloxone (an opioid antagonist) blocked the desire for cannabinoid drugs, and the CBI antagonist SR 141716 A blocked morphine self-admin-istration. These results point to "mutual regulation between endogenous cannabinoid and opioid systems in the neurobiological control of reward."

• Mechoulam and colleagues reported finding high concentrations of 2-AG in mammalian milk, suggesting that cannabinoids might play a role in maternal-off-spring bonding, as well as in appetite stimulation.

• The cannabinoid receptor is coupled through the cell membrane to a G-protein, which transduces signals inside the cell. Howlett identified a peptide fragment on the CBI receptor, 14 amino acids long, that activates the signal transduction pathway inside the cell.

• Michelle Glass of the National Institute on Deafness and Other Communication Disorders determined that different conformations of the CB 1 receptor —induced by the various agonists — can be distinguished by different G-proteins within the cell. "It is possible," Glass concluded, "that by understanding the abilities of the receptors to couple to different G-proteins, and the ability of different agonists to direct this coupling, ligands may be developed that enable specific signal transduction pathways to be selectively targeted."

• Vincenzo Di Marzo, who previously had found that anandamide and 2-AG inhibit breast cancer cell proliferation in vitro by acting on CB 1 receptors, reported that the endqcannabinoids inhibit proliferation of prostate cancer cells by the same mechanism. They also inhibit the proliferation of cancer cells induced by nerve growth factor. Di Marzo concluded, "These findings suggest that novel anti-tumor drugs may be developed from these endogenous compounds."

• CBD has shown potential as an anticonvulsant in animals and an antiepilcptic in humans. Its antioxidant and neuroprotective properties were described at the 1998 ICRS meeting by Aidan Hampson of the National Institute of Mental Health, who determined that rats treated with CBD suffer milder damage when strokes are induced. This year Hampson examined the effect of CBD on enzymes that play a role in inflammation. (Inflamed nerve sheaths apparently play a role in stroke.) He found that CBD selectively inhibits lipoxygenases —some but not all of the subtypes — which make inflammatory mediators called leukotrienes.

Cannabinoids' Wide Impact

Bornheim describes the annual ICRS meeting as "a much more open, family type of thing compared to other conferences. You have a mixture of hard basic scientists, behavioral scientists, drug-abuse scientists, plus a few marijuana advocates who attend as well. Everybody sort of tolerates each other; there's very little ill feeling —as long as there's science there." Bornheim says that the past two ICRS conferences have left him with the impression that "cannabinoids are neuromodulators — they have some specific effects, but mainly they work by dampening the levels or activity of other systems. The NMDA receptor, adrenalin release, the GABA receptor, dopamine, the opioid system, pituitary hormone, prolactin, serotonin —virtually every system in the brain is impacted by the cannabinoids."

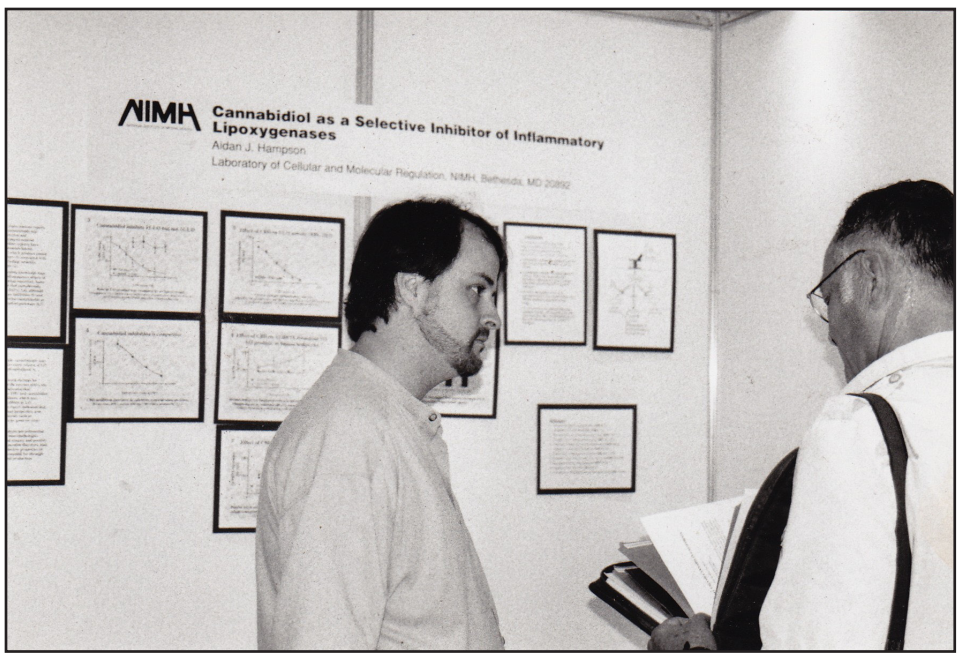
The fact that cannabinoids affect so many systems makes them more difficult to study and to develop thereapeutic drugs. "The FDA doesn't approve of polypharmacy in general," he observes. "To get a drug combination through the FDA is very difficult. And here you're talking about something with hundreds of different compounds and you have to prove that every one of them is really safe. If a drug company came up and said 'We're making this therapeutic with 100 different compounds and it's effective,' the FDA would say, 'Let's see toxicity data on every single one.'

"It gets down to the basic difference between Western medicine and Eastern medicine. Eastern medicine uses herbal extracts with hundreds of different compounds and they believe that the combination has value. Western medicine says, 'If it works, there's probably one component that's doing the job and everything else is complicating the issue. Let's find that ingredient. Let's make it 100 times more active with chemical substitutes, and then bombard the body and knock out the problem.'

"I'm not saying which one is right; that's how the two philosophies go. Marijuana clearly falls into the category of a holistic medicine; which isn't to say that you can't develop Western-style drugs from it. The advantage of the Western approach is its potential for selectivity —you can deliver to a single site."

In the 1970s more than 100 different cannabinoid metabolites were characterized in different animals. Their activity was determined by microinjection into the spine or directly into the brain ventricles, followed by measurement for analgesia or body temperature. Only 7-hydroxy-THC was found to be highly active. It is several-fold more psychoactive than THC itself, says Bornheim, who has found that brain levels of 7-hydroxy-THC are increased more than 10-fold after CBD pre-treatment. Interest in cannabinoid metabolites dwindled, Bornheim says, after only one proved to be active. Today only his lab and one in Japan arc dedicated to research in this area. If and when cannabinoid drugs go into clinical trials, however, interest may be renewed.

Captions:



Aidan Hampson of NIH has established that CBD has neuroprotectant properties. At right, Tod Mikuriya, MD