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The 2014 ICRS meeting was attended by 328 people —a record. Major pharmaceutical companies that used to send scientists to present papers and monitor the latest research—Abbott, Allergan, AstraZeneca, Bayer, Bristol-Myers Squibb, GlaxoSmith-Kline, Merck, Pfizer, Eli Lilly and Sanofi-Aventis—were not represented in Baveno. At least for now, Big PhRMA seems to have surrendered to the plant itself as a source of cannabinoid drugs.

The one exception was Hoffman-La-Roche. Researchers employed by the Basel-based giant have synthesized a drug with an extra-strong affinity for the CB2 receptor. It was found to greatly reduce the build-up of collagen (which obstructs the ureter) in a mouse model of kidney disease. "CB2 agonists might have beneficial effects in both acute and chronic kidney disease," the presentation by Jean-Michel Adam concluded.

The trend towards studying plant compounds and their possible therapeutic applications is largely attributable to GW Pharmaceuticals, a British company, founded in 1998, that has been developing plant-based medicines to treat various conditions.

The ICRS scientists' Holy Grail —even GW Pharmaceuticals'— is a drug that exerts the beneficial effects of cannabis without psychoactivity.

Thanks to GW providing materials and funding for studies of cannabidiol (CBD) and other so-called "minor cannabinoids," the virtual monopoly of the U.S. National Institute on Drug Abuse as sponsor of cannabinoid research has ended. But NIDA is still the biggest ICRS backer, and quite a few presentations in Baveno were devoted to "abuse potential" and other elusive adverse effects.

NIDA funds basic research

Mostly, NIDA provides funding for scientists doing important basic research in physiology and pharmacology. Over the years NIDA-funded scientists have figured out the mechanisms of action by which plant cannabinoids and endocannabinoids (made in the body) exert their effects and get metabolized (broken down).

This research continues in ever-finer detail at the molecular level. For example, in the late 1990s Dale Deutsch and colleagues at Stony Brook University identified fatty acid amide hydrolase (FAAH) as the enzyme that breaks down the endogenous cannabinoid anandamide within the cell. In recent years Deutsch's lab has focused on the fatty acid binding proteins (FABPs) that bring endocannabinoids from the cell membrane to the endoplasmic reticulum (where FAAH does its stuff).

Dale Deutsch reported that the molecules that transport anandamide and 2-AG from the receptor to the nucleus of brain cells — certain fatty-acid binding proteins— perform the same function for THC and CBD.
PHOTO BY ISTVAN UJVARY

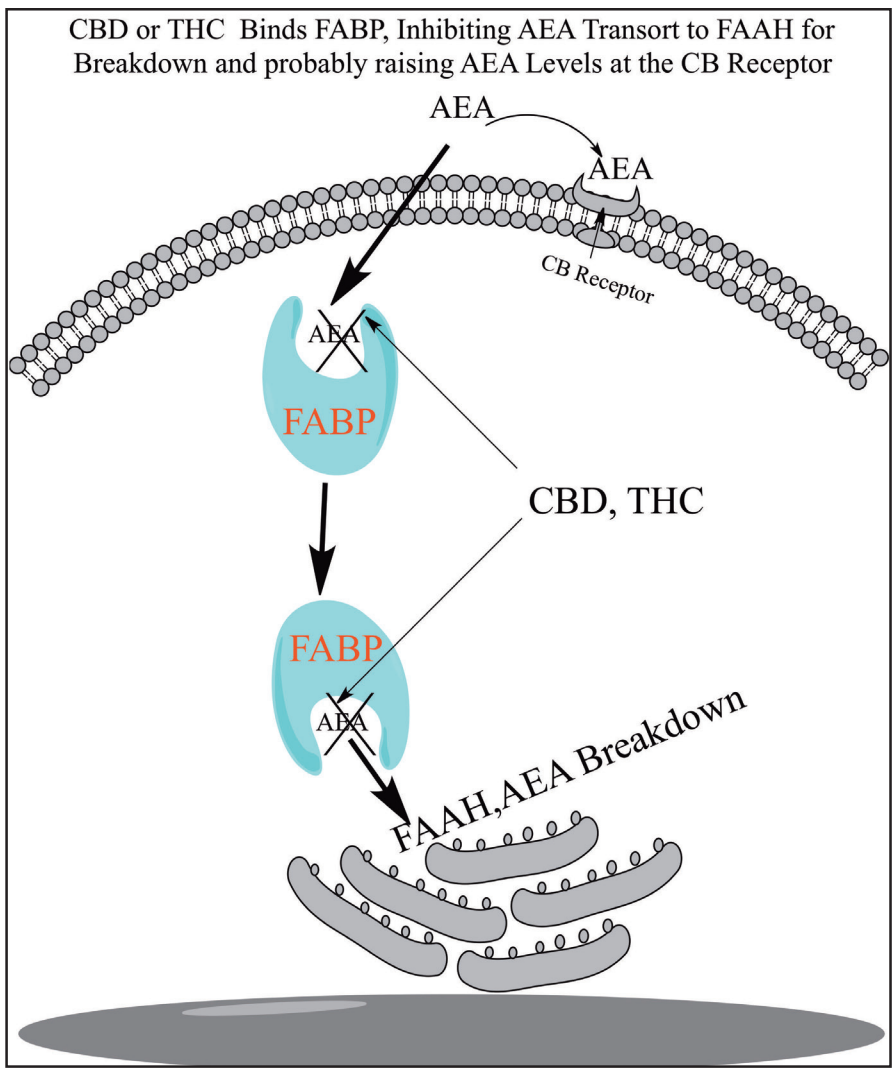
When plant cannabinoids are ingested by people smoking or eating marijuana, THC and CBD molecules are carried in the blood into the brain, "presumably by albumin and lipoproteins, which carry fats," says Deutsch. "But there's no albumin inside those cells in the brain."

In 2012 Deutsch's lab identified the molecules that transport anandamide (and perhaps 2-AG) in cells inside the brain: fatty-acid binding proteins —FABPs 3, 5, and 7 to be precise.

To determine if these very same fatty-acid binding proteins transport the plant cannabinoids THC and CBD, Deutsch reported this year in Baveno, his team did three kinds of experiments.

Simulations of molecular shapes, done by computational analysis, showed that THC and CBD "fit very nicely inside the fatty-acid-binding-protein carriers."

Binding studies using FABPs synthesized and purified in the lab showed that THC and CBD bind to these molecules as readily as anandamide and 2-AG do.



ANANDAMIDE (AEA) INACTIVATION results when CBD or THC targets fatty-acid binding proteins within the cell. At top, anandamide crosses the membrane by diffusion at the cannabinoid (CB) receptor. Once inside the cell, AEA requires fatty-acid binding proteins (FABPs) for transport through the cytoplasm to the endoplasmic reticulum (canoe-shaped structures), where it gets broken down by fatty acid amide hydrolase (FAAH). FABP inhibitors prevent anandamide from being delivered to FAAH for breakdown, resulting in increased anandamide levels at the receptor. Dale Deutsch and collaborators at Stony Brook University have identified the enzyme SB-FI-26 as a potent inhibitor of the FABP transporters.

Cell cultures confirmed that adding THC and CBD inhibited the uptake of anandamide and 2-AG —meaning they were binding to the same transporter molecules.

Deutsch also cited two human studies in which ingestion of THC or CBD was shown to increase anandamide levels in the blood because they act as anandamide -transport inhibitors. (See illustration above).

Deutsch's identification of FAAH as the enzyme that metabolizes anandamide inspired drug developers to create compounds that inhibit production of FAAH, resulting in elevated cannabinoid levels without ingestion of exogenous ("from without") THC. Fatty-acid binding proteins could also be drug targets, and their efficacy the topic of future ICRS talks.

Gender Distinctions

Cannabinoids are more potent analgesics in female rats than in male rats.

Rebecca Craft and MD Leitl reported in 2008 that the sex hormone estradiol enhances the analgesic effects of THC in females whose ovaries had been removed, whereas testosterone blocks the motion-reducing effects of THC in males.

At the 2013 meeting Aaron Haas, a postdoc in Craft's lab at Washington State University, presented a poster showing that estradiol increases sensitivity to THC's anti-pain effects, but testosterone does not.

A team of Israeli researchers led by Sharon Anavi-Goffer found a marked difference in the way male and female mice respond to postnatal administration of HU-267, a cannabinoid drug developed by co-author Raphael Mechoulam. ("HU" stands for "Hebrew University.") HU-267 is described as "a novel synthetic compound whose structure resembles that of ajulemic acid." The researchers gave the drug to mice of both sexes 24 hours after birth. They found that by 25 days of age, the males were more hyperactive while the females where more hypoactive compared with their control litter mates.

Now the researchers' goal is to figure out why this drug exerted gender-related effects. Its pharmacology is being elucidated in collaboration with Roger Pertwee.

Sexist Science Surpassed

At the 2014 meeting, Chris Breivogel, a pharmacologist at Campbell University in North Carolina, presented a paper called "Beta-arrestin2 appears to mediate the activity of cannabinoids in female mice in a manner that differs from males."

Beta-arrestin2 is a protein inside the cell that interacts with an activated cannabinoid receptor, and —it was thought by the scientists who isolated the molecule and put arrest in its name— blocks or dampens the signal.

Breivogel had previously shown that male beta-arrestin2 knockout mice (bred to lack the gene that encodes for beta-arrestin2) respond to THC more strongly than wild-type males.

Traditionally, experiments with rodents have been conducted with males.

His more recent studies, using female mice, "have shown very different effects from what was seen in males. The antinociceptive (but not rectal temperature) effects of THC obtained in wild-type females were nearly absent in beta-arrestin2 knockouts."

Traditionally, experiments with rodents

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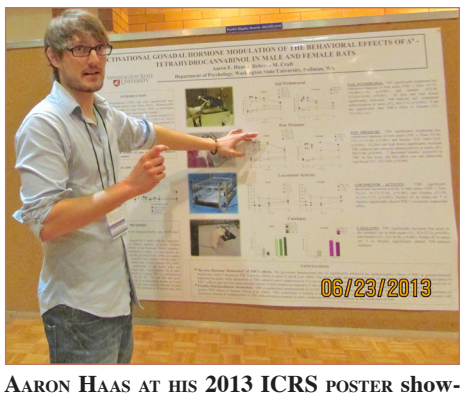

Aaron Haas at his 2013 ICRS poster showing that estradiol increases sensitivity to THC but testosterone does not.

Changing of the Guard among ICRS sponsors is reflected on page from the conference abstract book, although the U.S. National Institute on Drug Abuse remained the biggest backer of the organization (and of sanctioned cannabinoid research). A decade ago ICRS sponsors included major pharmaceutical companies. In 2014 GW Pharmaceuticals and Otsuka (a Japanese company allied with GW) were next, followed by Tilray, one of 13 Canadian companies licensed to cultivate.