None Will Take the High Road

# Cannabinoid Researchers Meet in Scotland

**By Fred Gardner**

The International Cannabinoid Research Society (ICRS) held its 18th annual symposium in late June, 2008, under the craggy Cairngorm Mountains in Aviemore, Scotland.

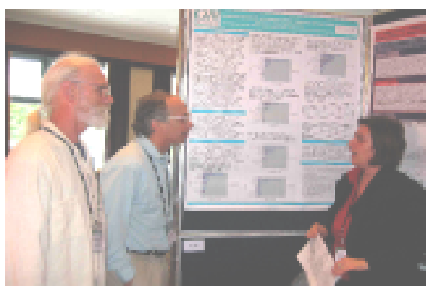
More than 200 scientists affiliated with universities and/or pharmaceutical companies presented papers and/or posters, and more than 100 other researchers attended. At least half were women. Labs from all over the world participated.

*ICRS scientists accept the constraints of cannabis prohibition.*

ICRS scientists appreciate the medicinal properties of the plant, but they accept the constraints of cannabis prohibition. Their practical goal is to develop drugs that exert certain beneficial effects of the plant – countering nausea, inflammation, malignancy, bone loss, etc.– without inducing "euphoria" or other alterations of thought or mood. Their research has yet to yield a blockbuster drug but it has led to the discovery and elucidation of the endocannabinoid system.

Since the ICRS was founded in 1990, its members have identified two agonists produced in the body —anandamide and 2-AG– which work as chemical counterpunches, sent from cells that are receiving chemical signals to cells that are transmitting them (to modulate the rate of transmission).

Researchers have identified at least



**Ethan Russo (center) discusses his poster with Barbara Costa and Jeff Hergenrather.**

two kinds of receptors (protein molecules on the outside of certain cells) activated by these endocannabinoids. The CB1 receptor is concentrated in the brain, and the central and peripheral nervous system. CB2 is found in tissue associated with the immune system, in the brain, and in nerve tissue associated with disease states causing inflammatory change.

There is strong evidence that other endogenous agonists and receptors exist.

Since anandamide has cannabis-like effects, one approach to designing a legal, cannabis-like drug involves blocking production of the enzyme that breaks down anandamide —fatty acid amide hydrolase, or FAAH. Less FAAH means more anandamide available at the synapse.

"Endocannabinoid Modulation of Pruritus" was one of many papers touting the promise of FAAH inhibitors. Investigators from Virginia Commonwealth University reported that mice made to itch by injection of a mast-cell degranulator, "Compound 48/80," would reduce their scratching if given a FAAH inhibitor called URB597.

Equally important, the mice wouldn't get high. "The FAAH inhibitor URB597 reduced the response to Compound 48/80 scratching without the increased hypomotility associated with CB1 receptor activity."

Similarly, investigators led by Sandor Batkai of the National Institutes of Health have found that URB597 and another FAAH inhibitor, AM-3506, lower blood pressure in rats by preventing the breakdown of anandamide. Ingesting herbal cannabis would have the same effect on blood pressure, but... "Because inhibition of FAAH does not elicit behavioral effects predictive of addictive potential, FAAH inhibitors such as AM-3506 may be considered for treatment of hypertension."

Why don't bolstered anandamide levels lead to psychoactive effects? FAAH inhibitors apparently work only on systems in the body where anandamide is being actively produced, whereas ingesting THC activates CB1 receptors throughout the body. A concern is that the FAAH enzyme interacts with compounds other than anandamide, and blocking its production might lead to unforeseen side effects.

**Basic Science Ultimately Pays Off**

At this year's ICRS meeting, Patricia Reggio of the Center for Drug Discovery, University of North Carolina Greensboro, showed a computer simulation of 2-AG being released from a "post-synaptic" cell and moving across the synapse to a CB1 receptor embedded in the membrane of the transmitting cell. Instead of penetrating the CB1 binding pocket from without, according to Reggio's amazing graphic, 2-AG penetrates the cell membrane near the receptor and then shimmies into the binding pocket from within the membrane and delivers its chemical message. Very sexy stuff.

Considerable buzz was generated by a report by Raphael Mechoulam and Itai Bab of Hebrew University in Jerusalem that a byproduct of anandamide, oleoyl serine, which has been found in brain and bone, shows phenomenal efficacy in promoting bone growth and slowing bone resorption.

Mechoulam said he deduced that the body would make oleoyl serine by applying "nature's law of stinginess." If a truly effective drug to treat osteoporosis

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# Enzymes and the Endocannabinoid System

**By Martin Lee**

Recent studies have shown that it is possible to attenuate a wide range of pathological conditions by preventing or delaying the enzymatic breakdown of endogenous cannabinoids. Scientists envision the development of hybrid drugs that target both cannabinoid receptors and metabolic enzymes as a new strategy for treating disorders that lack adequate therapies.

Enzymes are vital proteins within the body that are necessary for all biological functions, including the synthesis and degradation of endogenous cannabinoids and other neurotransmitters. All metabolic processes that occur within the body require enzymes to take place. Without enzymes, we simply would cease to function.

In 1996, Ben Cravatt and his associates at Scripps Research Institute in San Diego identified fatty acid amide hydrolase (FAAH) as the primary enzyme responsible for the rapid deactivation of anandamide, the endogenous cannabinoid that stimulates CB1 receptors, which are concentrated in the mammalian brain. A year later, scientists found another catalytic enzyme, FAAH-2, which is also involved in the breakdown of anandamide. FAAH-2 is present in higher mammals, but not in mice or rats.

On the basis of these discoveries, scientists have set their sights on the development of drugs that prolong the effects of anandamide by suppressing FAAH. This prolongation process is analogous to the activity of serotonin-reuptake inhibitors, such as Prozac, which treat depression by delaying the breakdown of serotonin and making it more available to stimulate serotonin receptors in the brain.

Researchers are enthusiastic about the therapeutic potential of synthetic FAAH-inhibitors such as URB579, which may be useful for treating a wide range of conditions mediated by the CB1 receptor. By raising anandamide levels, FAAH-inhibitors indirectly trigger the CB1 receptor –without generating the psychoactive "side effects" (the high) associated with marijuana.

Anandamide and THC both activate the CB1 receptor, but THC is more potent than its endogenous cousin. Enzymes metabolize anandamide very quickly; thus its duration of action is shorter than THC's. An anandamide buzz is more like a runner's high –indeed, exercise has been shown to elevate anandamide levels.

*Keith Sharkey disclosed that drugs targeting endocannabinoid degradation relieved experimentally induced colitis.*

Several new developments regarding FAAH-inhibitors were reported at the 2008 ICRS conference in Scotland. A Virginia Commonwealth University team reported that FAAH suppression reduced itching and scratching among rodents with experimentally induced pruritus. University of Calgary scientist Keith Sharkey disclosed that drugs targeting endocannabinoid degradation relieved experimentally-induced colitis. And Sandor Baktai at the U.S. National Institute of Health found that URB597 lowered the blood pressure of hypertensive rats, suggesting that FAAH inhibition may provide a remedy for hypertension.

The results of animal experiments are not always applicable to human conditions, but marijuana smokers may be heartened by a recent study conducted by Matthew Hill and a team of psychologists at the University of British Columbia in Vancouver. Hill concluded that the pharmacological blockade of FAAH promoted learning acquisition and cognitive flexibility in rats during a water maze experiment. Although Hill did not refer explicitly to cannabis at the ICRS conference, his research indicated that "the facilitation of anandamide/CB1 receptor signaling" via FAAH inhibition enhances cognitive performance. Given that cannabis stimulates CB1 receptor signaling, the implications of this study should not be too difficult to figure out, even if you don't smoke pot.

**A cure for the blues**

In 2007, Daniele Piomelli, director of the Center for Drug Discovery at the University of California, Irvine, reported that URB597, a synthetic FAAH-inhibitor which boosts the levels of the brain's anandamide, can help reverse symptoms of depression in rats. Piomelli's group gave URB597 to chronically stressed rats that act in ways similar to depressed people. Clinical trials with URB597, which Piomelli's team has patented, began in 2008 to ascertain this drug's efficacy as a treatment for depression.

Since antiquity, natural healers have used many plants to treat people suffering from anxiety and depression. Fabien Vincent and Margaret Nguyen (with In Vitro Pharmacology in the S.F. Bay Area) have demonstrated that extracts of a dozen medicinal herbs inhibited FAAH activity in biochemical and cell-based assays.

A poster at last year's ICRS conference summarized their research, which indicated that St. John's Wort and a dozen other herbs blocked FAAH. This study provides a clue as to why holistic healers often recommend St. John's Wort for depression; it also provides a theoretical basis for understanding how St. John's Wort functions as an antidepressant. By inhibiting FAAH, St. John's Wort boosts anandamide levels, which mitigates the blues.

*CBD, by inhibiting FAAH, amplifies the subtle natural high of anandamide. This may qualitatively affect how a cannabis consumer experiences the psychoactivity of THC.*

A team of Italian researchers led by Tiziana Bisogno was the first to point out that cannabidiol (CBD), a crucial bioactive component in fiber hemp as well as in cannabis, functions as a FAAH inhibitor. In 2005, Ethan Russo and his colleagues at the Skaggs School of Pharmacy in Missoula, Montana, documented that CBD's anti-anxiety and antidepressant effects, which have been confirmed by several studies, are also mediated by CBD's direct activation of 5-HTIA serotonin receptors. Brazilian scientists provided corroborating evidence of a CBD-serotonin connection at the

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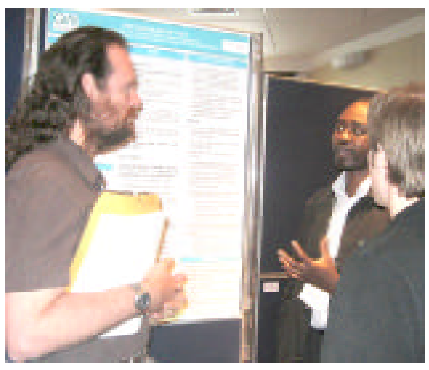
## *Cannabinoid Researchers* *from page 15*

–a natural product– goes on the market in about eight years, you read it here first. Ditto a Nobel Prize for Mechoulam's role in discovering Anandamide and, long before that, the chemical structure of delta-9 THC.

Another offshoot of basic research was described by Christopher Fowler, who studied the role of the endocannabinoid system in prostate cancer. The prognosis in prostate-cancer cases –how advanced and fast-moving the cancer is deemed to be– determines whether invasive treatment is called for.

Fowler and colleagues at Umea University in Sweden hypothesized that the expression of CB1 receptors in response to prostate cancer growth would indicate how likely the cancer was to metastasize. They studied preserved tissue samples that had been removed from patients with enlarged prostates, the course of whose cancers was known. They measured the amount of CB1 protein present in the tissue samples and found higher levels in those with poorer prognoses. Doctors and prostate-cancer patients may in the future take into account CB1 level in making treatment decisions.

A final point from Fowler, et al: The proliferation of CB1 receptors triggered by aggressive prostate cancers implies that such cancers may be treatable by cannabinoids. "Given that the endocannabinoid system can affect the invasivity of prostate cancer tumor cells in vitro, its modulation may be a possible therapeutic approach for prostate cancer."



**The Potential of CBD**

The evidence that CBD has important medical uses continues to pile up. One of its uses is to counter the psychoactive efffects of THC.

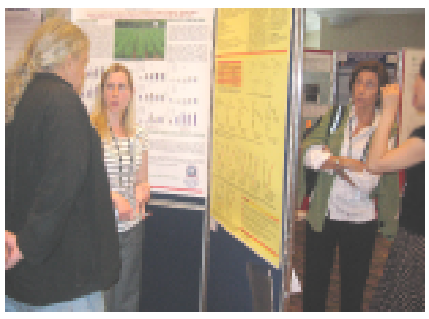
At ICRS 2008 Philip Robson of Oxford University, Dept. of Psychiatry, and GW Pharmaceuticals, reviewed psychiatric adverse events in the records of 496 MS patients who had received Sativex and 434 who received placebo. Sativex, a mix of CBD and THC, induced adverse events at a low rate –disorientation (5.4%), depression (3%), dissociation (2.8%), hallucinations (1.8%), confusional state (1%), and paranoia (.8%). Anxiety and insomnia occurred more frequently following placebo.

"There was no evidence from these studies that Sativex poses any long-term psychiatric risks to patients," Robson and co-author Tilden Etges concluded. "The presence of CBD may inhibit some unwanted effects of THC."

• A team led by Michael Cawthorne of the Clore Laboratory, University of Buckingham, reported on "The Metabolic Effects of THCV and CBD." THCV is a cannabinoid produced by the plant that is an antagonist at the CB-1 receptor.

The investigators conducted a five-week trial treating genetically obese mice with purified THCV, purified CBD, and a 1:1 mix of the two. The mix was most promising. The THCV exerted a thermogenic effect (increased energy expenditure) while the CBD raised plasma HDL-cholesterol concentration and reduced liver triglyceride levels.

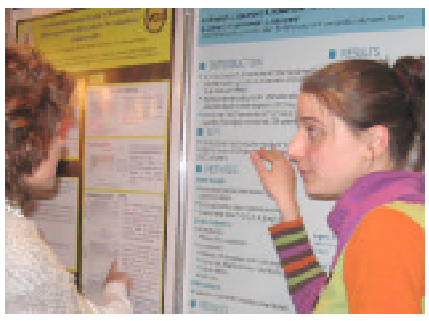
"This is the first demonstration of potential beneficial effects of CBD in hypercholesterolaemia and non-alcoholic fatty liver disease," the authors concluded. "In combination with THCV, it potentially addresses a number of components of the metabolic syndrome."



• Saoirse O'Sullivan of the University of Nottingham, Derby City General Hospital, looked at the vascular effects of CBD on rat aorta isolated in vitro. She had previously shown that THC has a relaxant effect that is partially inhibited by the antagonism of a putative third CB receptor. This year she concluded, "CBD causes significant vasorelaxation over time... The majority of the vasorelaxant effects of CBD appear to be through calcium channel inhibition."

• A team of Spanish and Scottish researchers used a piglet model of hypoxic-ischemic encephalopathy (brain damage due to insufficient oxygen, which affects an appalling number of premature babies and for which there is no specific treatment). They concluded, "Administration of CBD alone after HI reduced brain damage and was associated with extracerebral benefits." The intellectual duplicity of prohibition is exposed by the presence of non-psychoactive CBD on Schedule 1 (dangerous drugs with no medical potential). CBD modulates the effects of THC by an unknown mechanism. It may be an antagonist at a putative third cannabinoid receptor.

• Several investigators are trying to figure out how cannabinoids exert anti-tumor effects. An Italian group studying "Inhibition of Human Glioma Cell Migration and Invasiveness Induced by Cannabidiol" found that CBD inhibits production of an enzyme (Matrix Metalloproteinase-2) required for tumor growth.

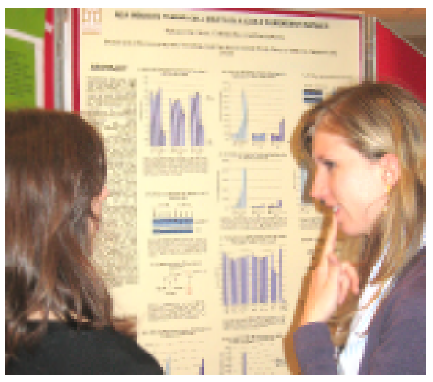


• "CBD Ameliorates Cognitive Impairments Associated with a Model of Chronic Liver Disease in Mice" –the title sums up the results reported by Iddo Magen of the Hadassah Hebrew University Medical School. The structure of CBD, Magen noted, "resembles that of resveratrol, which is found in red wine and has anti-inflammatory activity. Resveratrol has also been shown to decrease liver oxidative stress."

*GWP will produce and screen for biological activity plant extracts in which "minor" cannabinoids predominate.*

Geoffrey Guy, MD, the founder of GW Pharmaceuticals, observed in a post-conference interview, "CBD was considered a 'minor cannabinoid' when we started looking at it. Now it's the focus of considerable research." Studies sponsored by GW have already established the medical potential of THCV and CBG (Cannabigerol). The company has a three-year plan to produce plant extracts in which other "minor" cannabinoids predominate, and, in concert with Otsuka scientists, to screen their components for biological activity. "We've got to stop thinking of the targets for phyto-cannabinoids as 'cannabinoid receptors,'" says Guy. "We should be asking 'Which receptors are activated by the plant polyphenols?'"

Clearly there is more to cannabis than just THC. There are other components —"minor" cannabinoids, terpenoids and flavonoids— that affect our bodies through various mechanisms and might be developed into useful medications. The field of cannabis therapeutics is just opening up.



**Living Proof: Kristen Peskuski**

William Courtney, MD, made the trip to Scotland from Ukiah, California, with a living poster –his partner, Kristen Peskuski, who was then almost five months pregnant. They attributed her relatively good health to megadose cannabinoid intake, including the ingestion of raw leaf, which is rich in THC-A, the acid form of THC.

In her youth Peskuski was diagnosed with juvenile rheumatoid arthritis, then lupus, then interstitial cystitis. Debilitated by pain, she was bedridden for four years and treated ineffectively with steroids, painkillers, anti-inflammatories, and a slew of toxic chemicals to kill the nerves in her bladder. On six occasions she was put under general anesthesia and her bladder was dilated with water (to destroy the nerves). She underwent numerous surgeries. Diagnosed with cervical cancer, she had 2/3 of her cervix removed at age 26. She was told she was sterile and that she would have to adopt if she ever wanted children.

Courtney and Peskuski will attend the 2009 ICRS meeting with their healthy six-month-old, Zahiya. Courtney has submitted a poster on the original functions of the protein that has evolved into the CB1 receptor. Peskuski will give an autobiographical oral presentation, "Putative Aberrations of the Endogenous Cannabinoid System: a Case Study."

**Kristen Peskuski, William Courtney**

## *Enzymes* *from page 15*

2008 ICRS conference.

It has long been understood that CBD, the second most prominent cannabinoid in cannabis, is not psychoactive like THC. But CBD, by inhibiting FAAH, amplifies the subtle natural high of anandamide, and this, in turn, may qualitatively affect how a cannabis consumer experiences the psychoactivity of THC.

**Fine-tuning our inner cannabis**

Scientists have identified several enzymes involved in the biosynthesis and deactivation of 2-Arachidonyl-glycerol (2-AG), an endocannabinoid that stimulates both CB1 and CB2 receptors. (THC also activates both receptors, whereas anandamide only activates CB1.)

Discovered three years after anandamide, 2-AG is the most abundant endocannabinoid in the brain and is involved in many physiological processes, including neuroprotection, immune cell proliferation, analgesia, and appetite regulation. 2-AG is rapidly metabolized by monoglyceride lipase (MAGL) and at least three other degradation enzymes (ABHD6, ABHD12 and NTE) that were recently detected by Nephi Stella, at the University of Washington.

Studies are currently underway to determine whether the inhibition of MAGL, the major player in the control of 2-AG levels, is an appropriate target for pharmaceutical intervention. Researchers are hopeful that the inhibition of MAGL may convey some of the therapeutic benefits of cannabis while avoiding the plant's politically incorrect psychotropic effects.

One of the great rewards of being a member of the International Cannabinoid Research Society is that clinicans and academic researchers can share their findings and ideas. At the ICRS meeting in Scotland I had the opportunity to discuss with Keith Sharkey and Karen Wright the benefits of whole-plant cannabis in treating Crohn's disease in humans. (I have been monitoring the progress of 22 such patients.)

The university-based scientists do experiments in test tubes and on mice and conduct clinical trials in humans with the goal of developing single-molecule cannabinoid medicines. I can describe to them the effects I've observed, and they can update me on the likely mechanism of action.

In relieving inflammatory bowel disease, cannabis enhancement of natural cannabinoid functions brings the body into homeostasis by turning down the inflammatory reactions, pain and spasms of overstimulated nerve pathways. The tendency to cancerous transformations is reduced.

One approach to achieving beneficial effect is to slow the degradation of the natural endocannabinoids with a resultant up regulation of the cannabinoid function in the bowel. Given the safety profile of cannabis, the researchers are not anticipating adverse side-effects.

Single molecule medicines may prove to be very useful, especially when the psychoactive effects of cannabis are undesirable. *–Jeffrey Hergenrather.*

In songbirds and people

# Cannabinoids Involved in Language Acquisition

**By John McPartland**

Anthropologists wonder what catalyzed the "great leap forward" in human behavior that began about 50,000 years ago. Although modern Homo sapiens evolved about 150,000 years ago, fully modern behavior did not emerge until about 50,000 years ago.

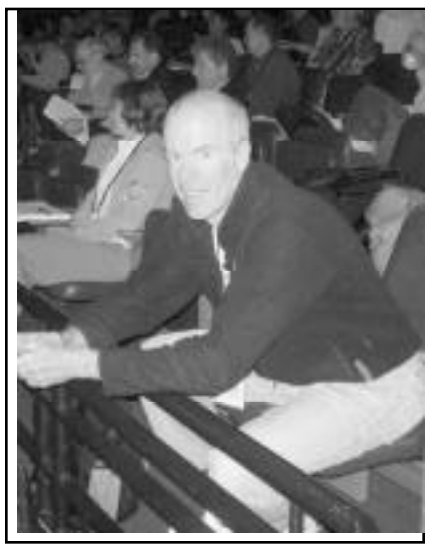
Jared Diamond, a physiologist at the UCLA Medical School, proposed in *The Third Chimpanzee* (1991) that language triggered the "Great Leap Forward." In his subsequent best-seller, *Guns Germs and Steel* (1997), Diamond described the "great leap" as a series of smaller steps.

The first archaeological evidence of modern behavior emerged in East Africa, with standardized stone tools and the first jewelry. But when humans migrated out of Africa to Asia and Europe, suddenly we see evidence of new tools out of new materials (eg, fishhooks from bone, spear handles from wood, rope from hemp), new art media (such as cave paintings, pottery, musical instruments), and evolved intricate social (and religious) organizations.

What caused the sudden improvement in language skills? Diamond proposed an anatomical change in the voice box or the organization of the human brain. Other scientists hypothesize it was positive selection precipitated by a favorable mutation in FOXP2, a gene associated with language development.

Perhaps it was a change in the environment. Environmental change may invoke positive selection in a new gene allele, giving rise to physiological or anatomical changes, or in humans, new behaviors.

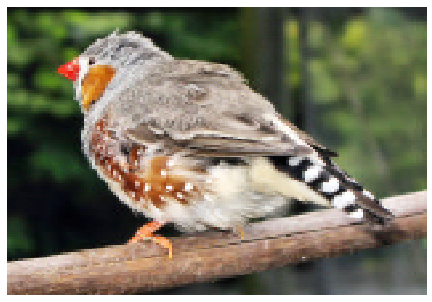
*Was cannabis the catalyst that synergized the emergence of syntactic language and opened the door to greater consciousness?*



**John McPartland**

Humans create their own environmental changes. For example, when Neolithic Europeans domesticated livestock, they profoundly changed the ecological landscape as well as their own nutritional environment. The novel nutritional environment selected for a single nucleotide polymorphism (SNP) in the lactase enzyme gene, a favorable mutation that gave rise to lactose tolerance – an advantageous trait for milk drinkers (Bersaglieri et al., 2004).

Could an environmental factor in Asia and Europe have triggered the great leap forward? Terrence McKenna, in *Food of the Gods* (1992) suggested that ingestion of Psilocybe species enhanced human language ability. McPartland and Guy in *The Medicinal Use of Cannabis* (2004) proposed that Cannabis was the catalyst that synergized the emergence of syntactic language and opened the door to greater consciousness in Mesolithic humans. Pollen studies indicate that Cannabis grew in Asia as well as Europe at least 40,000 years ago, so the interaction between humans and Cannabis was possible.



**The "finch guy"**

Professor Ken Soderstrom has published interesting work regarding endocannabinoid system evolution. Shortly after anandamide was discovered, Soderstrom's group showed that the endocannabinoids have a deep evolutionary history, based on their presence in extant organisms. These included a very primitive animal, the sponge (Mycale micracanthoxea), as well as the sea kelp Saccharina angustata (formerly Laminaria angustata), and even a blue-green algae, Lyngbya majuscula (Soderstrom et al., 1997).

Soderstrom's group also accessed deep-level phylogenetic signals in cannabinoid receptors. They were the first to clone CB1 from a non-mammal, the amphibian Taricha granulosa (Soderstrom *et al.*, 2000). They also characterized CB1 in a bird brain, the zebra finch, Taeniopygia guttata (Soderstrom et al., 2001). Zebra finch CB1 is highly expressed in the same brain regions as human CB1, and is activated by cannabinoids and blocked by rimonabant.

Song learning by the zebra finch shares many behavioral and neurological similarities with human language acquisition. Both humans and zebra finches learn vocal behavior during sensitive developmental periods (approximately childhood and adolescence), during which species-specific vocalizations are stored in memory and subsequently used to guide speech development. Most other birds and mammals do not need prior exposure to species-specific vocalizations to produce them.

*Song learning by the zebra finch shares many behavioral and neurological similarities with human language acquisition.*

At ICRS'08, Soderstrom turned his attention to the expression of the FOXP2 gene in zebrafinch brain. FOXP2 expression is greatest in the cerebral cortex, striatum, basal ganglia, cerebellum, thalamus –areas enriched with co-expressed CB1.

When Soderstrom injected zebra finches with the synthetic cannabinoid WIN55212-2, the treatment significantly increased FOXP2 expression in the brain! Acute treatment with WIN upregulated FOXP2 expression in both adults and adolescents, whereas chronic WIN exposure continued to upregulate FOXP2 in adolescents but not adults. Note that FOXP2 upregulation is not generated by other drugs, such as alcohol and morphine, at least not in mice (MacLaren et al., 2006; Korostynski et al., 2007).

Taken together, this body of work suggests that CB1 activation in humans consuming Cannabis may enhance the expression of FOXP2. It doesn't take a big leap of conjecture to scroll backwards 50,000 years and propose that exposure to Cannabis triggered the great leap forward by human hunter-gatherers.

**Ken Soderstrom**

## Backgrounder

The identification of genes that shape human-specific traits has captured the imagination of researchers around the world. What genes separate humans from chimpanzees, whose genomes are otherwise 98% identical?

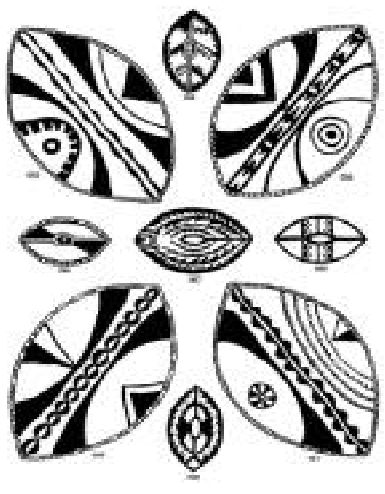
One candidate, the FOXP2 gene, is associated with the acquisition and use of language in humans. Others include MRGX2 (a nociception-specific gene), KLK8 (a gene preferentially expressed in the central nervous system), and two genes associated with brain size, ASPM and MCPH1.

Human versions of these genes differ significantly from chimp versions. The human genes show signs of positive selection, which arises when a gene mutation provides its carrier with a selective advantage.

McPartland et al. (2007) investigated genes encoding the endocannabinoid system for evidence of human-specific traits. Positive selection was calculated as "Ka/Ks," the ratio of nonsynonymous nucleotide substitutions to synonymous nucleotide substitutions, normalized to that expected under neutral evolutionary divergence. Although evidence for positive selection was found in genes encoding endocannabinoid ligand enzymes (e.g., PTPN22, DAGLA, NAPE-PLD), the genes for CB2 and especially CB1 were under strong purifying selection. Purifying selection arises in genes that have been selected for optimal function for millions of years. Thus mutations in these genes reduce carrier fitness and they are usually removed from the population.

*What genes separate humans from chimpanzees, whose genomes are otherwise 98% identical?*

The gene for DAGLA, encoding the 2-AG precursor enzyme, showed an exceptionally strong signal of positive selection. Why 2-AG and not anandamide? Perhaps the adaptive pressure driving positive selection has been human exposure to tetrahydrocannabinol (THC). THC antagonizes the activity of 2-AG and not anandamide (Straiker and Mackie, 2007). This scenario parallels results by Rockman et al. (2005), who attributed positive selection in the PDYN promoter (precursor molecule for endogenous opioids) to ancient use of plant opiates.



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At least for the time being

# Adieu, Rimonabant

## Failure of weight-loss drug was foreseen by pro-cannabis MDs

In November 2008 the European Medicines Agency (EMEA) ordered Sanofi-Aventis to stop selling Rimonabant, a drug that reduces appetite by blocking cannabinoid receptors in the brain. Some 700,000 people had taken Rimonabant, which was marketed in the UK and elsewhere as Acomplia.

Data from ongoing clinical trials showed that Rimonabant users suffer depression, anxiety, insomnia and aggressive impulses at twice the rate of subjects given placebo. In one study there were five suicides among Rimonabant users compared to only one among subjects on placebo. Finally the EMEA said "Enough" in a dozen languages.

A month earlier, Merck had abruptly canceled five clinical trials of a similar cannabinoid-blocker called Taranabant. The pattern of adverse psychiatric effects had become too obvious to conceal from U.S. and European regulators.

*Researchers at the MD Anderson Cancer Center reported that mice on rimonabant develop potentially cancerous polyps at a higher rate than controls.*

Regulators were concerned about Rimonabant use leading to an uptick in other illnesses that the cannabinoid system helps to suppress. In August researchers at the MD Anderson Cancer Center reported that mice on Rimonabant develop potentially cancerous polyps at a higher rate than controls.

**Dangers Were Foreseen**

The dangers of drugs that block cannabinoid receptors were foreseen by California doctors who monitor cannabis use by large numbers of patients.

Jeffrey Hergenrather, MD, of Sebastopol, California, was first to go public with his misgivings. Hergenrather had attended the 2004 meeting of the International Cannabinoid Research Society meeting at which Sanofi scientists reported that Rimonabant had proven safe and effective in clinical trials involving 13,000 patients. That year the ICRS's achievement award went to three Sanofi researchers. Only a few ICRS membrers expressed misgivings –off the record, please– about the basic approach.

Hergenrather and Dr. John McPartland were lonely voices questioning the propriety of Sanofi's march to the market. "The consequences of interfering with the cannabinoid receptor system have not been evaluated in normal human physiology," Hergenrather stated in *O'Shaughnessy's* (Fall 2004).

Hergenrather suggested that before Sanofi marketed Rimonabant, "It would be ethical to design longitudinal studies to assess the consequences of interfering with the cannabinoid system."

It makes sense that doctors treating patients who augment their cannabinoid levels (by smoking or otherwise ingesting cannabis) would be sensitive to the effects of blocking the receptors they activate.

Hergenrather's pro-cannabis colleagues shared his misgivings about Rimonabant. He and the late Tod Mikuriya, MD, both wrote letters to the U.S. Food and Drug Administration advising against approval. To FDA's credit, a panel of physicians would unanimously turn down Sanofi's application in 2007. (Their decision was influenced by the belatedly revealed dangers of Vioxx.)


**ACOMPLIA'S LAST ACCOMPLISHMENT, getting approved as a drug for which the UK National Health Service would reimburse, was announced in a Daily Mail headline on the day the 2008 ICRS meeting began in late June. Five months later the weight-loss drug would be pulled off the European market for safety reasons.**

The receptors blocked by Rimonabant are prevalent in areas of the brain responsible for emotional control. Why did Sanofi and the scientists who jumped on the Rimonabandwagon think they could depress cannabinoid activity in the limbic system without depressing mood? How did they rationalize their hope that a cannabinoid-antagonist drug would not reverse the beneficial effects of natural cannabinoids?

Some hypothesized that when the CB1 receptor is blocked, the endocannabinoids are redirected to other targets. They spoke hopefully of "compensatory mechanisms" that would kick in.

**A positive side effect?**

Phil Denney, MD, saw a silver lining in the Rimonabant marketing drive. He figured it would serve to educate U.S. doctors about the cannabinoid receptor system, which was discovered in the late 1990s, and has not made it into the medical school curriculum.

Denney called his SCC colleagues' attention to a two-page Sanofi ad in the *Journal of the American Medical Assocation,* touting "A newly discovered physiological system... The Endocannabinoid System (ECS)."

The *JAMA* ad was one of about a dozen that Sanofi ran in medical journals to explain Rimonabant's mechanism of action. It said that the endocannabinoid system "consists of signaling molecules and their receptors, including the cannabinoid receptors (CB1 and CB2)." The CB1 receptors are "located centrally in the brain and peripherally in liver, muscle and adipose tissue" and "may assist in regulating physiologic processes, e.g., lipid and glucose metabolism."

But the gusher of enlightenment that Denney anticipated sputtered out quickly. Sanofi did not succeed in defining "Metabolic Disorder" as a real disease the way Eli Lilly had with "Clinical Depression." A nation that had been educated about the serotonin reuptake process did not get equivalent instruction about the cannabinoid receptor system. The information contained in a few medical-journal ads never crossed over into the mass media.

In most of the stories dealing with the rise and fall of Rimonabant, reporters avoided the term "cannabinoid receptor system" entirely. For example, in Jeanne Whalen's Oct. 24 *Wall St. Journal* piece about the EMEA withdrawing approval, she described Rimonabant as "a new kind of drug that blocks receptors in the brain that help control food intake."

In March 2007, when the FDA was evaluating Rimonabant, Whalen wrote a front-page piece with this doubly inaccurate phrase: "Cannabis, the active ingredient in marijuana, acts on the same receptors..."

I wrote a polite note to the editor explaining that "cannabis" and "marijuana" are synonyms, and that the plant contains more than one active ingredient. Ms. Whalen emailed back: "Thanks for writing — always good to hear from readers. I actually didn't mean to get that technical in my phrasing — I was really just saying that the drug marijuana is made from cannabis. But thank you for the points you made. Best regards, Jeanne Whalen."

This woman covers the European pharmaceutical industry for the *Wall St. Journal!*

Has any honor accrued to Hergenrather and the SCC doctors who joined in warning that Rimonabant would induce serious adverse side-effects? Of course not, they can be marginalized as "potdocs."

Soon after Rimonabant was taken off the market in Europe, Hergenrather had to write a letter to a Butte County judge who would not allow a patient of his to medicate with cannabis while on probation unless the patient got a second approval from an orthopedist.

The patient was a middle-aged construction worker with a well-documented history of back pain for which he had been hospitalized, treated by chiropractors, acupuncturists, osteopaths, and physical therapists, and prescribed Celebrex, Flexeril, Soma, Valium, Vicodin, Percodan, Percocet, Darvocet, Ultram, ibuprofen, naproxen, etc.

Not only was the judge playing doctor, she didn't understand that orthopedists have no expertise treating pain. Dr. Hergenrather put this much more diplomatically in his letter to her –as diplomatically as he put his warning about Rimonabant in the summer of 2004.

## ICRS 2009: Examining More Facets of CBD

Papers to be presented at the 2009 ICRS Meeting in Pheasant Grove, Illinois, July 8-11, included:

• Cannabidiol as a Novel Inhibitor of ID-1 Gene Expression in Aggressive Breast Cancer Cells by McAllister et al.

• Anticonvulsant Effects of Cannabidiol Upon Spontaneous Epileptiform Activity in Acute Hippocampal Brain Slices by Jones *et al*.

• Cannabidiol as a Novel Anti-Acne Agent? Cannabidiol Inhibits Lipid Synthesis and Induces Cell Death in Human Sebaceous Gland-Derived Sebocytes by Biro *et al*.

• Cannabidiol May Act as a 5-HT1A Auto-Receptor Agonist to Reduce Toxin-Induced Nausea and Vomiting by Rock *et al*.

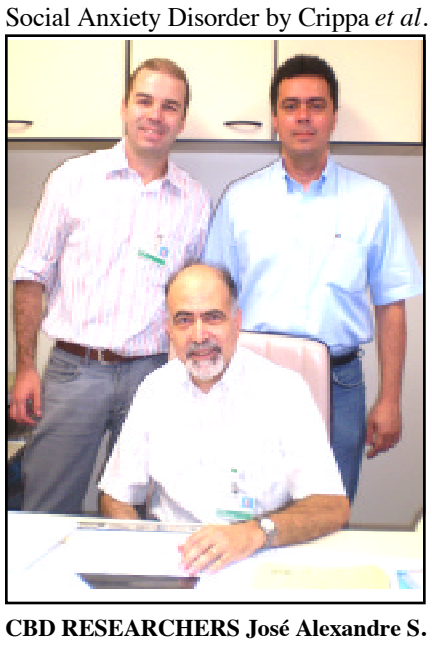
• Cannabidiol Controls Intestinal Inflammation Through the Modulation of Enteric Glial Cells by DeFilippis *et al*.

• Characterization of the Neuroprotective Effect of Cannabidiol After Oxygen and Glucose Deprivation of Newborn Mice Foregrain Slices -Romero et al

• The Effect of Cannabidiol and delta-9 THC On Social Interaction of Rats by Malone *et al*.

• Cannabidiol Reduces Lipopolysaccharide-induced Vascular Dysfunction in the Mouse Brain: An Intravital Microscopy Study by Ruiz-Valdepenas *et al*.

• Neural Basis of Anxiolytic Effects of Cannabidiol (CBD) in Generalized Social Anxiety Disorder by Crippa *et al*.



**CBD RESEARCHERS José Alexandre S. Crippa (standing, left), Antonio Waldo Zuardi (seated) and Jaime E. C. Hallak, Department of Neurosciences and Behavior; Division of Psychiatry, Ribeirão Preto Medical School, University of São Paulo, Ribeirão Preto SP, Brazil and INCT-Tranlational Medicine, Brazil**

Dr. Crippa and colleagues have used single-photon emission computed tomography (SPECT) to study what happens in the brain when a subject experiences anxiety. He reports, "The anxiolytic-like effect of CBD in healthy volunteers was observed in a recent double-blind study that investigated its effects on regional cerebral blood flow... Because the procedure itself can be interpreted as an anxiogenic situation, it allows the evaluation of anxiolytic drug action. CBD induced a clear anxiolytic effect and a pattern of cerebral activity compatible with an anxiolytic activity."

In collaboration with Philip McGuire's lab in London, Crippa's team employed functional magnetic resonance imaging (fMRI) and "observed that CBD affected activation when subjects were processing intensely fearful stimuli, attenuating responses in the amygdala and cingulate cortex. The suppression of the amygdalar response was correlated to the drug effect of reducing fluctuations of skin conductance. Therefore, similar to the data obtained in animal models and results from studies in healthy volunteers, these results strongly suggest an anxiolytic action of CBD."