Danger! Danger! Danger!

Cannabinoid Antagonist Drug Will be Marketed for Weight Loss

By Fred Gardner

Sanofi, a multinational pharmaceutical company based in France, is planning to market a weight-loss drug called Rimonabant that works by blocking part of the cannabinoid receptor system.

Scientists employed by Sanofi reported at the 2004 meeting of the International Cannabinoid Research Society that Rimonabant has proven safe and effective in clinical trials involving 13,000 patients.

Sanofi expects FDA approval within the year. The fact that Rimonabant blocks the "euphoric" effects of marijuana is a big plus in the eyes of U.S. government regulators.

The marketing is already done, in a sense, because everybody knows that marijuana induces the munchies, and it seems logical that blocking the cannabinoid receptors would reverse the effect.

But the advent of Rimonabant troubles California doctors who have made a specialty of monitoring their patients' cannabis use, as well as some scientists who are studying the basic nature of the cannabinoid system.

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—Jeffrey Hergenrather, MD

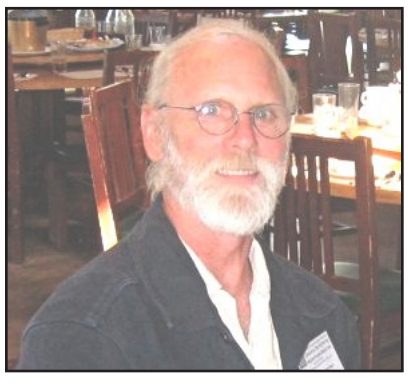
Jeffrey Hergenrather, MD, of Sebastopol —one of the few clinicians to attend this year's ICRS meeting— warns, "We are only now becoming aware of the modulating effects the cannabinoids have on the body and mind. The consequences of interfering with the cannabinoid receptor system have not been evaluated in normal human physiology."

Some Definitions

Cannabinoid receptors are proteins on the surface of certain cells to which certain compounds bind, setting off molecular cascades within the cells that produce effects in the body such as reduced inflammation, increased appetite, etc.

Two kinds of cannabinoid receptors have been discovered —CB_1, which is highly concentrated in the brain and central nervous system, and CB_2, found mainly in tissues associated with the immune system.

There are three different kinds of cannabinoids, or chemical "agonists" that activate the cannabinoid receptors. They are, in order of evolutionary appearance: compounds made in the body for purposes of neurotransmission, compounds unique to the cannabis plant (the most famous being delta-9 THC), and compounds made in the lab —synthetics.



Jeffrey Hergenrather, MD: California Cassandra? (She's the Godess doomed to foresee the truth and be ignored.)

Cannabinoids made in the body are called "endocannabinoids" (the prefix is a contraction of "endogenous," just as the body's endogenous morphine-like chemicals are called "endorphins").

The first endocannabinoid to be identified —by Raphael Mechoulam and William Devane in 1992— was named "anandamide" after the Sanskrit word for "bliss."

It has since been learned that endocannabinoids help regulate the cardiovascular, digestive, endocrine, excretory, immunological, nervous, reproductive, and respiratory systems.

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Rimonabant is an "antagonist" drug that engages the CB_1 receptors so they can't be activated. Originally called SR-141716, it was developed by Sanofi in the early '90s as a tool for researchers investigating the endocannabinoid system. If a given effect is blocked by SR-141716, that effect is said to be "mediated" by CB_1 receptors.

Being able to determine which metabolic effects involve CB_1 receptors was a huge step forward for ICRS scientists. In recent years, numerous talks and posters have described what happens when SR-141716 is administered to rodents. Sure enough, appetite suppression was observed consistently.

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Now Sanofi is conducting clinical trials involving large numbers of people. a talk at the ICRS meeting entitled "Clinical Results with Rimonabant in Obesity," Sanofi researcher Gerard Le Fur reported that the drug had done well in phase-three clinical trials involving 13,000 patients.

The trials were conducted at numerous sites in the U.S. Obese patients were treated with Rimonabant for 52 weeks. "Over 72% of patients at 1 year showed a weight loss of greater than 5 percent, with over 44% showing a weight loss of greater than 10%," according to Le Fur. "There was also an increase in HDL-cholesterol values, a reduction in triglyceride values and reductions in glucose and insulin values... The general tolerance of the compound was excellent."

The negative remarks were anecdotal or speculative; the positive data belonged to Sanofi.

Your correspondent asked Sanofi researchers how a drug could block the CB_1 receptor system without adversely affecting mood, sleep, pain relief, and other CB_1-mediated aspects of well-being. The answers were vague —other neurotransmitters may play compensatory roles. We were told that no pattern of adverse effects had been observed during the clinical trials, and that such effects are probably so rare that they won't be detectable until Rimonabant has been used by millions of people over a period of years.

The developer of another antagonist drug, a rival of Sanofi's, claimed that Rimonabant induced anorexia ("food aversion") in five percent of the test subjects. Le Fur responded that obesity was such a widespread and serious health problem that five percent seems like an acceptable rate of anorexia.

From the perspective of the scientists in the ICRS —mainly employees of universities or pharmaceutical companies who get funding from the U.S. National Institute on Drug Abuse— it's a win-win-win to honor Sanofi for developing CB-receptor antagonists as "new therapeutic drugs."

Other criticisms and misgivings were only whispered. A multiple sclerosis specialist told of a case in which Rimonabant apparently caused an immediate, extreme exacerbation. A physician wondered —since the body's own cannabinoids have neuropro-tectant and anti-oxidant functions—if Rimonabant users would be at increased risk for stroke and cancer. But the negative remarks were anecdotal or speculative; the positive data belonged to Sanofi.

Le Fur and two colleagues accepted the ICRS's 2004 achievement award on behalf of their company. It was presented by Mechoulam himself, the grand old man of the field, who observed that Sanofi had shown great foresight in developing a weight-loss drug in the 1990s, because it has since swallowed up two much larger drug companies, Synthelabo and Aventis.

From the perspective of the scientists in the ICRS —mainly employees of universities or pharmaceutical companies who get funding from the U.S. National Institute on Drug Abuse— it's a win-win-win to honor Sanofi for developing CB-receptor antagonists as "new therapeutic drugs." NIDA is eager to sponsor research involving cannabinoid antagonists. A lot will be learned about the cannabinoid system, its mechanism of action, etc. And a therapeutic effect is a therapeutic effect, whether it's produced by activating or blocking the cannabinoid receptors.

But common sense and a few cautious clinicians say *DANGER DANGER DANGER!* CB_1 receptors are concentrated in the cerebellum and the basal ganglia (responsible for motor control, which may help explain why marijuana eases muscle spasticity in disorders like multiple sclerosis), the hippocampus (responsible for storage of short-term memory), and the limbic system (emotional control). Although other neurotransmitters may play compensatory roles when the cannabinoid receptors are blocked, the longterm impacts will not be known until years after Sanofi gets approval to market Rimonabant to the pizza-loving masses. Before marketing commences, says Hergenrather, "It would be ethical to design longitudinal studies to assess the consequences of interfering with the cannabinoid system."

Other uses for cannabinoid-antagonist drugs are being studied with encouragement from NIDA. Walter Fratta of the University of Cagliari gave a paper in Paestum proposing antagonists "as

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Sanofi Rechercheurs Honored

Murielle Rinaldi-Carmona, Francis Barth, and Gerard Le Fur, scientists working for the French pharmaceutical giant Sanofi-Aventis, were honored at the 2004 ICRS meeting for developing a drug that blocks cannabinoid receptors. Originally intended for research purposes, this "antagonist" drug is going to be marketed as for weight loss and under the name "Rimonabant" (derived from the name of the principal investigator).

ICRS 2004

therapeutic agents to prevent relapse to heroin abuse." Carl Lupica of NIDA discussed Rimonabant as a "potential treatment" for food, alcohol and nicotine cravings. "It is also clear that marijuana craving may be successfully treated by this drug," he said pointedly.

G.W. still waiting for approval

Alas, this was supposed to be the year that G.W. Pharmaceuticals won the ICRS achievement award and hosted the big party. G.W. is the British firm that in 1998 got government approval to develop and test an extract of the cannabis plant which it formulated as an oral spray and dubbed "Sativex."

Clinical trials of Sativex as a treatment for neuropathic pain, multiple sclerosis and other conditions were conducted and favorable results reported to the regulators. Bayer agreed to market Sativex in Europe when the approval came through. G.W. generously made Sativex and other plant extracts with different cannabinoid contents available to investigators who previously could experiment only with synthetics or plant material from NIDA.

But the marketing approval that Guy said he expected by the end of 2003, and then by spring '04, has yet to be granted. So he and his associates had to walk a bit of a tightrope in Paestum, reassuring all concerned that Sativex certainly will get approved, while not risking any more misstatements about when.

Guy cited favorable data produced in recent trials of Sativex as a treatment for pain in rheumatoid arthritis and spasticity in multiple sclerosis. G.W. researcher Ethan Russo presented a paper showing that patients taking Sativex achieve beneficial effects without requiring increasingly large doses, i.e., tolerance does not build up.

Unfortunately, in the U.K. as in the U.S., favorable trial results can count for less than the establishment connections of the doctors who conduct them. And so the British regulatory authorities continue to ponder G.W.'s dossier, while the banquet at this year's ICRS meeting was hosted by Sanofi.

"Beneficial Effects" Takes Back Seat

Russo's talk was one of three given on "Beneficial Effects" at the end of the last day. The auditorium in which more than 400 conference participants had listened to earlier speakers held about 50. Beneficial effects seemed more like a quaint afterthought than an urgent goal.

Russo's report was significant. He and three colleagues had looked at data from various trials in which subjects had used Sativex, GW's 50-50 mixture of high-THC and CBD plants formulated for spraying under the tongue for 600 patient-years. "Consistent maintenance of symptom control (pain, spasm, sleep, bladder disturbances) with stable or even diminishing CBME dosages was noted. Sativex in chronic adminsitration demonstrates a favorable side-effect profile in comparison with standard medicines for neurogenic symptoms, with no tolerance developing to its clinical benefits."

Sanofi's Gerard Le Fur (right) played down fears of adverse side effects from Rimonabant. In background, Peter McLaughlin.

Sebastopol general practitioner Jeffrey Hergenrather, MD, described the health history questionnaire developed by the California Cannabis Research Medical Group [previewed in the Spring 2004 *O'Shaughnessy's*] to facilitate data collection and research. California patients have reported that cannabis helped ease the symptoms of more than 100 conditions not referred to in the pre-1937 medical literature.

The net effect of virtually all the funding going to people who are trying to develop synthetics, or "elucidate the basic mechanism" by which the receptor gets activated, is to deflect research away from the plant itself.

Tomi Jarvinen of the University of Kuopio, Finland, reported that THC, anandamide and other natural cannabinoid agonists could be made more water-soluble by formulating them as phosphate esters or cyclodextrins. As in so many of the earlier talks, the beneficial effects Jarvinen was referring to will be delivered at some time in the future. And people are hurting in the now.

Scientific conferences are divided into talks and posters. The talks are 15 minutes; speakers can use all their time to describe their research or leave a few minutes for questions. Everyone shows slides, and many simply read the same text that's being shown on the slides.

When we first attended an ICRS meeting in '98, there were 63 posters; this year there were 155, which shows how the field is burgeoning. As in previous years, the brilliant young researchers we talked to expressed confidence that relying on the U.S. National Institute of Drug Abuse for funding won't undermine their objectivity or induce them to search for adverse effects. They're conducting useful basic research that will explain the body's endogenous cannabinoid system and lead to useful new drugs.

And yet the net effect of virtually all the funding going to people who are trying to develop synthetics, or "elucidate the basic mechanism" by which the receptor gets activated, inducing a chain of chemical events inside the cell is to deflect research away from the plant itself.

As a biochemistry postdoc at UCSF (where not a single investigator studied plants) told us in '98, "If you care about cost-effective treatment for individuals, then you would be in favor of the classic natural cannabinoids. However, if you care about drugs that optimally treat the various conditions, then you start looking at receptor distribution and maximizing activity and things like that."

Being partial to those classic natural cannabinoids, we were interested in a poster by Benjamin J. Whalley and coworkers at the University of London's School of Pharmacy: "A Novel Component of Cannabis Extract Potentiates Excitatory Synaptic Transmission in Rat Olfactory Cortex In Vitro."

It may turn out that one of the terpenes that give cannabis flowers their smell is also exerting an effect on the mind and body.

Smell Matters

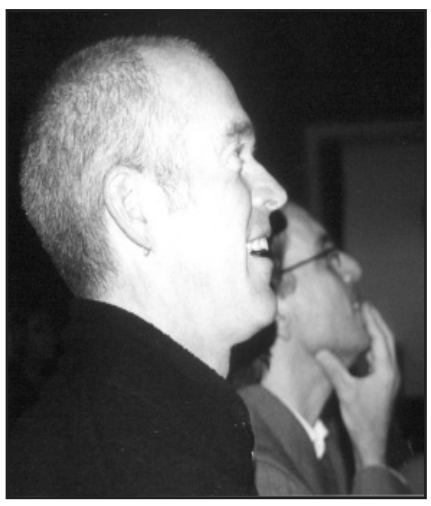
Whalley et al. worked with a "standard cannabis extract" —meaning whole buds turned into a liquid by a strong blender— from which they removed the delta-9 THC by chemical means. They found that the THC-free extract had a excitatory effect on nerve cells taken from the nose of a rat (whereas THC has a suppressive effect). They know that the mystery component is working through CB_1 receptors because its effect can be blocked by the cannabinoid antagonist SR141716A. The authors infer that a "novel compound" is active in the plant, it does not appear to be CBD, and its potentiating effect at the synapse appears to be *greater* than THC's.The authors conclude, "The potentiating effects and enhancement of cell excitability of the unkown extract constituent(s) on neurotransmission were capable of over-riding the predominantly suppressive effects of delta-9-THC on excitatory neurotransmitter release. This phenomenon may possibly explain the preference by some patients for herbal cannabis rather than isolated delta-9-THC (due to attenuation of some of the central delta-nine-THC side effects) and even account for the rare incidence of seizure episodes in some individuals taking cannabis recreationally."

Geoffrey Guy (right) and Ethan Russo of G.W. Pharmaceuticals: the victory lap has been postponed.

It may turn out that one of the terpenes that give cannabis flowers their smell is also exerting an effect on the mind and body. Smell matters —and not just cosmetically.

Krysztina Monory was a co-author on a poster by Federico Massa and lead author on another, "Mechanism of Cannabinoid Receptor-Dependent Protection Against Excitotoxicity." She is trying to figure out exactly how anadamide and CB1 receptors are involved in protecting against nerve damage in mice.

Massa's group showed that the endogenous cannabinoid system protects against colonic inflammation "both by dampening smooth muscular irritation caused by inflammation and by controlling cellular pathways leading to inflammatory responses."



John McPartland of GW Pharmaceuticals (with Vincenzo Di Marzo, the ICRS president-elect, in background).

Betty Yao of Abbott Laboratories. More than 10 major drug companies sent representatives to the ICRS meeting.

Arriving to set up posters: Federico Massa and Krysztina Monory of the Max Planck Institute of Psychiatry in Munich.