

## An Overview at the IACM meeting in Cologne

## Mechoulam on Cannabidiol

The emerging significance of cannabis components other than THC was again a prominent theme when the International Association of Cannabis as Medicine met in Cologne in early October, 2007. The IACM was founded in 1997 by Franjo Grotenhermen, MD (as the German ACM); it is a smaller organization than the ICRC and its focus is more clinical, less pharmacological.

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Raphael Mechoulam of the Hebrew University, Jerusalem, Faculty of Medicine gave a talk on cannabidiol on the occasion, he noted, of his 45th year of involvement in the field. In October, 1962 Mechoulam had just gotten his PhD in chemistry and was looking for a research project that might lead to tenure at the Weizmann Institute. He chose to analyze the components of cannabis, he said, thinking "it's a minor project, it will be finished off in six months."

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Hashish of Lebanese origin was obtained from the police —"There is a fantastic collaboration between Arabs and Jews in smuggling," Mechoulam observed— and a dozen constituents were then identified by two types of chromatography. (Some cannabis constituents had been identified previously, including CBD, which Roger Adams of the University of Illinois isolated in the early 1940s.)

Mechoulam and his co-workers elucidated the exact chemical structure of CBD in 1962 and of THC the following year. It was generally assumed for almost two decades that the cannabinoids exerted effects not by binding to a specific receptor but "nonspecifically" by altering the lipid structure of cellular membrane. Mechoulam established that the action was specific by purifying THC and showing that only the natural version of the molecule—and not its synthetic mirror image— was exerting the effect.

In 1988 Alynn Howlett found that THC was indeed activating a receptor. It was dubbed "CB1" and was found in those areas of the brain involved in movement, stress, cognitive function —"everywhere it would be expected," said Mechoulam, given what was known about the effects of cannabis on people.

"A receptor doesn't exist in the brain just because there's a plant out there," Mechoulam reasoned, "chances are there are endogenous compounds that will act on these receptors—so we went after them."

Whereas others were looking for peptides, Mechoulam figured the CB1 receptor would be activated by

a lipid. Sophisticated analytical techniques and brilliant, dedicated lab workers ("They should not be married so they can work 24 hours a day, seven days a week") enabled Mechoulam to isolate a cannabinoid produced by the body itself—arachidonoyl-ethanolamide or AEA, which his colleague William Devane dubbed "anandamide," incorporating the Sanskrit word for "bliss."

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Mechoulam's lab isolated a second endogenous compound, arachidonyl glyceride, or 2-AG, which is more abundant in the body but less potent than anandamide. Although their structures are different, AEA, 2-AG and THC have similar pharmacological effects.

The receptors to which they bind weave in and out of the cell membrane and are coupled to a protein that triggers events within the cell leading to slowed release of neurotransmitters. (Think of a tiny doorknob twisting on the outside of a frenzied beehive and starting a sequence of events on the inside that results in fewer bees departing the hive.)

Because the cannabinoids affect the intensity with which other neurotransmitters are firing, they modulate numerous systems within the body. Mechoulam said, "There is almost no physiological system that has been looked into in which endocannabinoids don't play a certain part."

Unlike THC, CBD hardly binds to the CB1 receptor. It binds to a second cannabinoid receptor—CB2—originally found in spleen cells by S. Munro of Cambridge University in 1993 and subsequently found in the stomach, liver, heart, kidney, lymph and immune cells, bones, endocrine glands, and throughout the peripheral nervous system.

In his IACM talk Mechoulam reviewed research in recent years that has shed light on aspects of CBD's mechanism of action. Its lipid-solubility enables it to get into places in the brain that conventional neurotransmitters cannot reach. It is a potent anti-oxidative agent. It turns out to be an *antagonist* to a recently discovered receptor called GPR-55 to which THC and 2-AG bind as agonists. It blocks the uptake of adenosine, an inhibitory neurotransmitter that may promote sleep. It blocks the formation of various cytokines (signaling compounds not released by nerves or glands) under certain circumstances. It activates

the serotonin receptors. No wonder, then, that CBD plays a role in many clinical conditions.

**Conditions treatable by CBD**

Mechoulam described an experiment led by Paul Consroe and colleagues in Brazil in which CBD was tested as a treatment for intractable epilepsy. Patients stayed on the anticonvulsants they had been on (which hadn't eliminated their seizures) and added 200mg/day of CBD or a placebo. Of the seven patients getting CBD over the course of several months, only one showed no improvement; three became seizure-free; one experienced only one or two seizures, Mechoulam recalled; and two experienced reduced severity and occurrence of seizures.

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"So it seemed a very promising approach," said Mechoulam, "but unfortunately, nothing has been done ever since. To the best of my knowledge, nobody has done any work on cannabidiol in the clinic on epilepsy, and I just wonder why."

A colleague of Mechoulam's, Marc Feldman at Imperial College, London, tested CBD on mice who had a version of rheumatoid arthritis and found that it reduced inflammation by almost 50% at the right dose—5mg/kg of body weight. But this "beautiful antiinflammatory reaction was lost if we went up to, say, 25 mg/kg," Mechoulam said. Drug developers must bear in mind and cope with the fact that cannabinoids have a finite "therapeutic window"—they are ineffective at low and high doses.

**CBD for Diabetes**

Mechoulam has been testing CBD on mice bred to have a version of type-1 diabetes that manifests around age 14 weeks. He and his co-workers treated these mice with CBD for their first 6-7 weeks of life, then tested them 6-7 weeks later and found that only 30% had developed diabetes (compared to 90-100% given placebo).

*CBD did not just prevent onset but blocked development of diabetes.*

In a follow-up experiment the mice weren't given a course of CBD until age 14 weeks, when they were developing diabetes. They were then tested at age 24 weeks, and again only 30% of the treated mice were found to have diabetes. In other words, CBD did not just prevent onset but blocked development of diabetes.

Examination of the insulin-producing islets showed that only 8% were intact in the untreated diabetic mice, whereas 77% were intact in the mice treated with CBD. "I believe that here we have something very promising," Mechoulam said. "We plan to have a clinical trial starting next week treating patients, and hopefully at the next meeting I will tell you that all of them are cured."

**"Let's have some more CBD"**

Cardiologists working with mice at Hebrew University have found that CBD treatment at the time of a heart attack can reduce infarct size by about 66%. "So now they're pushing me, 'let's have



photo by Alon Weinstock

more CBD," Mechoulam said. "We should try it with humans in a few years."

He went on: "What about sleep? I'm jumping from thing to thing to show you that CBD does quite a lot of things and I'm not sure that all of them are according to the same mechanism."

Mechoulam was part of a group led by Eric Murillo-Rodriguez that administered CBD to rats and determined that while THC caused sleepiness, CBD increased wakefulness and significantly decreased REM sleep. According to Mechoulam, "When one says 'cannabis causes sleep,' one should think really of two compounds, one that causes sleep and one that causes awakening."

**Anti-nausea**

The anti-nausea and memory extinction effects of CBD "seem to be closely related," Mechoulam said. He described the problem of anticipatory nausea, for which no good drugs are available. (The effects of chemotherapy can be so nauseating that patients start vomiting when they see the doctor or nurse who is going to administer the treatment.)

Linda Parker at the University of Guelph conditioned shrews to start vomiting by administering lithium fluoride at a certain location. When the shrews were subsequently placed in that location they began vomiting. But if given CBD, they could be moved to the dreaded location without vomiting. [THC is anti-emetic, too; the advantage of CBD in this instance may be legal rather than medical.]

"The conditioned-wretching reaction was completely abolished," Mechoulam declared. "Can we abolish other kinds of conditioning?"

He described an experiment in which rats had a choice of two paths, one leading to cocaine. Rats like cocaine (and amphetamine) and will learn to choose the path leading to it. But if injected with CBD, they no longer show a preference for cocaine!

Mechoulam characterized post-traumatic stress disorder, certain phobias and forms of chronic pain as "human situations which are conditioned" and might be amenable to treatment with CBD. "I know that many patients with PTSD take cannabis, self administered," Mechoulam said. He has been trying to interest the Israeli Ministry of Health in testing CBD and THC at various ratios to treat PTSD.



At the IACM meeting: Mechoulam and Christian Steup, director of THC-Pharm, a Frankfurt company that synthesizes CBD and other chemicals for clinical and research purposes.