New Hope in the War on Zits

Cannabidiol as a Treatment for Acne?

Accutane is one of the deadliest drugs in the aptly named "armamenture" of Western medicine. Could a cannabis-based medicine be safer and more effective in treating acne? At the 2009 ICRS meeting, Tamas Biro gave an intriguing talk entitled "Cannabidiol as a Novel Anti-Acne Agent? CBD Inhibits Lipid Synthesis and induces Cell Death in Human Sebaceous Gland-Derived Sebocytes."

Acne involves the overproduction of sebum, a lipid (oily substance) excreted by the sebaceous glands to create waterproofing of the skin. Conversely, lipid production is too low in dry-skin conditions such as seborrhea, eczema and itching (which can lead to inflammation). It has been learned in recent years that the sebaceous glands and hair follicles (which also produce oil) have endocannabinoid receptors, as do the surface keratinocytes.

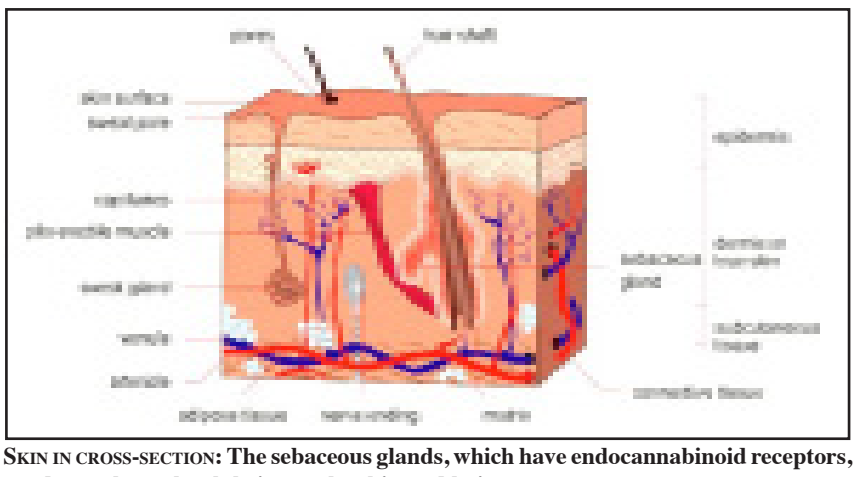
At his lab at the University of Debrecen (Hungary) Department of Physiology, University of Debrecen, Biro works with a line of cells derived from human sebaceous glands. Applying endocannabinoids to the cells, he observed, results in the CB2 receptors dramatically "upregulating" lipid production. Blocking the endocannabinoids with an antagonist drug dramatically suppresses lipid production. Biro wondered, "If the endocannabinoids are so important for the work of the sebaceous glands, how would phytocannabinoids affect that process?"

Biro started with CBD rather than THC for several reasons, he explained in an interview. "CBD is not banned in Hungary —there's no restrictions on its use, you can buy it from Sigma and other sources. Because it's non-psychoactive, if we turn up a potential good drug, it will be much easier to market with CBD." Moreover, CBD had been shown by Audra Stinchcomb at the University of Kentucky College of Pharmacy to penetrate the skin readily through a transdermal patch.

Biro and colleagues applied CBD to cells that had been treated with anandamide, expecting that CBD would further stimulate lipid synthesis. "To our surprise," he recounted, "Anandamide in the presence of CBD was unable to produce a lipid synthesis! CBD does exactly the opposite of the endocannabinoids. It does not stimulate but inhibits lipid synthesis, especially if the lipid synthesis was previously upregulated, as for example in acne. It was very surprising," he reiterated, "that a phytocannabinoid could prevent the action of the endocannabinoids."

Biro has been investigating the mechanism by which CBD works. His data show that CBD "does not target the 'classical' CB receptors but rather certain ion channels expressed on the sebocytes. When activated by CBD, these channels open and permit the influx of calcium to the cells which, in turn, inhibit lipid synthesis. We are working to elucidate the exact mechanism.

"Acne can also be considered as an inflammatory disease in which the skin within the zit is highly inflamed. We know from the literature that CBD has anti-inflammatory properties but it had never been tested on the skin cells. If it really works as an anti-inflammatory, then we would be getting two birds with one stone.



Skin in cross-section: The sebaceous glands, which have endocannabinoid receptors, produce sebum that lubricates the skin and hair.

"Acne is a human-specific disease. We don't have too much fur. Animals with fur may not need the oily cover for the surface of their skin because they don't have uncovered skin. No hair — only around the paw and the genitalia region, the nose, the very tips... Sebaceous cells from animals may operate differently than human ones. So there is no good animal model for acne."

Biro applies CBD in a methanol-ethanol solution. He is considering how best to formulate it for acne patients. "The vehicle should be the easiest possible," he said. "Think about the psychology of it. If you're a teenager you don't want to put creams on your face, you want a clear solution.

"There will be no trouble getting volunteers for clinical trials. Acne is not a life-threatening disease, but the impairment of quality of life is tremendous. You do not want to socialize. You close the door. It's your face! And the scars can establish an extreme cosmetic problem. The current medications are variably effective —topical gels combined with oral antibiotics and even hormone drugs for severe cases."

The average US incidence of acne is 10%. "Very difficult to say the actual cause," Biro says. " They call it a 'multifactorial' disease. Genetic background plays a role, hormones —that's why we see acne starting with adolescents as they enter puberty. There can be local inflammatory factors —some specific pathogens, the Propionibacteria that can accumulate and cause inflammation..."

Diet? "A fat-rich diet (chocolate is fat-rich) and extremely spicy foods —if the other factors are present. Some say even smoking can aggravate... Stress is an important factor. We say not only the eyes but the skin is the mirror of our soul and our spirit." Dermatologists studying the interaction of brain and skin, Biro says, "have found real mediators coming from the nervous system and acting on the skin cells."

We asked Biro about the possible anti-acne effects of THC —does THC stimulate lipid production in the skin, like anandamide, or decrease it, like CBD? He said it had not been studied, but was on his to-do list for 2010.

At the ICRS meeting in Chicago Biro met several other researchers interested in testing various cannabis-plant compounds. "We think CBG [cannabigerol] might have an effect [on lipid production]," he said. "Once you've found that there's something in the plant, why not see if there's other things in the plant that might be effective?"

CBD, he hastened to add, "is very efficient —actually, in our model system, it was much more efficient than the Vitamin A derivatives like Accutane. Of further importance, CBD was universally inhibitive of lipid synthesis. It was able to inhibit not only the actions of endocannabinoids but also the effects of other inflammatory mediators such as steroid hormones that stimulate fat production in these cells.

"Another important result: we found that low concentrations of CBD were very effective in inhibiting lipid synthesis but did not affect the viability of cells. This was also in contrast to the effects of Vitamin A derivatives which inhibit the fat production of sebocytes by killing them."

We asked Biro what happens to the normal cells surrounding the zit? He said, "We found that at the right non-toxic concentration, CBD doesn't suppress basal lipid synthesis in normal cells. Why bother those guys that are okay? It would create dry skin. Dry skin and itching —that's also impairment of quality of life. At the right concentration you get only the cells that are pathologically increased."

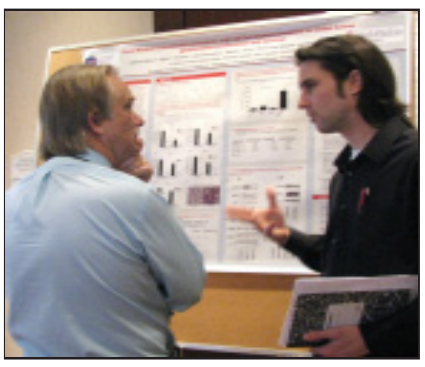
We also asked about baldness. "Currently, there is no effective treatment against hair loss," said Biro. "However, as we published before, THC and the endocannabinoid anandamide applied to cultured hair follicles were found to inhibit hair growth, most probably via the activation of CB1 in the hair follicle. In good accord with these data, a single animal study has shown that orally administered CB1 antagonists accelerated hair growth in mice. Perhaps someday a version of Rimonabant can be developed to promote hair growth."

ICRS Meeting *from previous page*

researchers Sean McAllister and Mary Abood —and he was romantically involved with Alex Franco, an organizer for Americans for Safe Access. Marcu and Franco are now married and living in Philadelphia, where he is doing research in the lab run by Abood (who moved from CPMC to Temple University Medical School.)

Marcu's poster at the ICRS meeting —which won the highest award given to grad students— was based on research begun with McAllister. It showed that a combination of THC and CBD is much more efficient at killing cells from an aggressive brain cancer, glioblastoma multiforme, than either cannabinoid on its own. Marcu got the idea to test cannabinoids in combination because the plant itself deploys them in combination, and he entitled his poster "Plant Wisdom: CBD Synergizes with THC to Inhibit GBM Proliferation and Survival."

Marcu explains, "Looking at chromatograms of plant samples, I noticed that certain cannabinoid ratios were showing up frequently. THC to CBD in a 10-to-1 ratio was very common. So I thought a 10-to-1 ratio would be more effective than either compound alone. Sean McAllister suggested that we start by testing the cannabinoids individually, and that's what we did —starting with the precursor compound CBG— to see how well they killed cancer cells in the petri dish."



William Courtney (left) and Jahan Marcu

Marcu measured the efficacy of THC and THC acid, CBD and CBD acid, cannabinol and cannabichrome. Then he started testing various combinations — "and that's when we started seeing surprising results," he recounts. "Doses that literally did not kill a statistically significant amount of cancer cells were suddenly obliterating everything in the petri dish in three days."

The most efficient combination turned out to be a 4-to-1 ratio of THC to CBD. Whether that THC-to-CBD ratio is optimal only in the case of one particular cell line, or holds true in treating other glioblastomas, or other cancers, remains to be studied.

Marcu, McAllister *et al* also determined that cannabinoids in combination kill cancer cells by a different pathway than cannabinoids acting solo. Marcu's analogy for the layman: "Instead of choking the victim, 'you hold his arms while I punch him in the stomach.'"

Individually or in combination, cannabinoids kill cancer cells by inducing apoptosis —"programmed cell death." Cannabinoids in combination induce apoptosis earlier in the cancer cell's life cycle —which is good news, given the goal of preventing metastasis.

Cannabinoids in combination kill cancer cells by a different pathway than cannabinoids acting solo.

The cells go through three phases: initial growth, synthesis of DNA, division. "Cancer cells grow and divide, grow and divide, and soak up all the nutrients around them," says Marcu. "You want to inhibit them in the growth phases, if possible. And that's what the combination of cannabinoids does, we found."

Marcu was outside smoking a cigarette when his first prize was announced at the ICRS awards banquet. "I have since tried to quit," he says ruefully. Marcu applauds the work of Antonio Luchini, the grad student whose presentation took second place. Luchini showed that inhibiting FAAH can reduce the cocaine reward response.

And the nicotine reward response?