

Stuart Tomc, Cannabinoid Educator: Staying in Step With the State of Research

Interview by Craig Gustafson

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Stuart Tomc, vice president of human nutrition at CannaVest, will discuss regulatory and compliance issues surrounding the clinical use of cannabinoids at the 2015 American Association of Naturopathic Physicians, August 5 through 8 in Oakland, California. Tomc is an authority on evidence-based dietary supplements with more than 20 years of experience in the field of nutritional medicine. He served as vice president of North American Herb and Spice, and he was a global educator for Nordic Naturals. Tomc has been interviewed on more than 4000 radio programs and dozens of television shows.

Integrative Medicine: A Clinician's Journal (IMCJ): Can you tell me when the endocannabinoid system was identified and how that research evolved?

Stuart Tomc: The endocannabinoid system was discovered just over 20 years ago and it has become the new darling target for drug developers, because the endocannabinoid system seems to be connected to our metabolic homeostasis. It is connected to our nervous system in a way that is very unique and interesting. It is connected to our circadian rhythm. There is not one organ system in the body that is not influenced, either directly or indirectly, by the endocannabinoid system.

Anandamide, coming from the Sanskrit word *ananda*, which means “joy, bliss, or delight,” is an endogenous cannabinoid neurotransmitter. It was isolated and its structure described in 1992 by W. A. Devane, Lumír Hanuš, et al, who were working in a team led by an Israeli scientist who is usually credited for discovering the endocannabinoid system: Raphael Mechoulam, PhD. Dr Mechoulam is considered to be the forefather of cannabinoid science. I would strongly encourage you to look him up and to look up some of his lectures.

The Israelis have been much further ahead in the area of research. However, let's remember that a lot of the funding, if not all of the funding, for Dr Mechoulam and his group and other researchers in Israel actually originates here in the United States with the National Institutes of Health, or NIH. So, here in the United States, indirectly, we are supporting the most progressive country in the world when it comes to cannabinoid research, and that is Israel.

IMCJ: Cannabinoids are most often considered in connection with the neurological system, but you mentioned that research has observed effects throughout the body. What are the common receptors and where are they found?

Mr Tomc: We have 2 primary endocannabinoid receptors and they are known as cannabinoid receptors 1 and 2, or CB₁ and CB₂. These are G protein-coupled receptors and they are located in the central and the peripheral nervous system; white blood cells; adipocytes, or fat cells; the liver; and bone. These receptor sites—and this whole system—are involved in learning and synaptic plasticity, immune regulation, appetite and pain, metabolic health and insulin sensitivity, and myriad other things.

It is much easier to sell the potential medical benefit of cannabis extracts if there is a simple, easy-to-digest marketing pitch. The simple pitch has been, “You have a CB₁ receptor and CB₂ receptor and there are these phytocannabinoids in nature and they are designed to interface with a system that is involved in homeostatic regulation of almost everything in the body.” There is misinformation and oversimplification of the endocannabinoid system promoting that these phytocannabinoids found in plant material are direct lock-and-key endocannabinoid matches as agonists to their respective receptors, meaning that they actually fit into these receptor sites directly.

The endocannabinoid system actually exists because we make endogenous marijuana-like compounds that are ligands—keys for these receptors. People who are very interested in the space of cannabis and cannabis extracts have extrapolated that if there are phytocannabinoids in nature, that somehow we were preordained to interface with these plants and/or to use cannabis. That is absolutely factually inaccurate. The fact that there are some structural similarities—and they are very minor similarities—between the way that the phytocannabinoids and the endocannabinoids interact with the cannabinoid receptors, that is just nature—biochemical coincidence, if you will.

We need to start focusing on what actually happens when we consume these phytocannabinoids and how they work in the body. That is something that we are just

starting to be able to fully elucidate. We do know, up to this point, that the plant-based phytocannabinoids do not have much affinity—if any affinity—for CB₁ and CB₂.

The exception to that would be tetrahydrocannabinol, or THC. THC has direct affinity for the CB₁ receptor. However, the other major cannabinoids, such as cannabidiol, or CBD, seem to work in a more complex way. It is likely that multiple mechanisms exist to control phytocannabinoid effects, including the direct “lock-and-key” model, as well as other G protein-coupled receptors involved, modulation of enzyme degradation, and receptor up- and downregulation. It is very exciting and we are still debating and trying to figure all this out.

Again, I think it is important to understand that we are still at the learning phase regarding how these phytocannabinoids work in the body and that we want to be very careful to not make sweeping generalizations with something that we are still learning about.

IMCJ: Is cannabis the only plant in nature that provides phytocannabinoids?

Mr Tomc: There are cannabinoid mimetics that are found in other compounds, but with the exception of some very rare plants that are found in Africa, the phytocannabinoids—of which there are 60 or 70 or, depending on who you follow, maybe up to 100 different compounds—that are showing the major potential benefit right now, THC and CBD, are only found currently in saleable quantities in *Cannabis sativa* or in other species of cannabis.

IMCJ: From what nutritional factors are endocannabinoids derived?

Mr Tomc: Endocannabinoids are produced from phospholipid precursors and the non-oxidative metabolism of polyunsaturated fatty acids, of which arachidonic acid is the principle one. This is an area that very few people are talking about, yet, that I know of.

The main endocannabinoid that gets talked about is anandamide. The endogenous, arachidonic acid-sourced neurotransmitter that we make on demand as need be can

also be stored. The other major endocannabinoid is called 2-arachidonoyl-glycerol, or 2-AG. Those are the main endocannabinoids, the physiological ligands for these cannabinoid receptors.

IMCJ: Are there nutritional cofactors that affect functionality of endocannabinoids?

Mr Tomc: There has been some suggestion that higher levels of the long-chain omega-3 fatty acids EPA and DHA may somehow help these G protein-coupled receptor sites and the lipid rafts become more optimized and more efficient. We have made some observations that people with high levels of omega-3, for example, seem to respond more vigorously and more favorably to serotonin selective reuptake inhibitors, or SSRIs. So there could be a very interesting dance here between the omega-3 and omega-6 balance and the CB₁ and CB₂ balance.

One of the theories that we have been working on is the possibility that we are getting overactive CB₁ activity associated with physiological states where we are metabolically compromised with overweight, prediabetes, insulin resistance, and abdominal obesity. Overactive CB₁ activity, or CB₁ dominant cannabinoid tone, can be driven by excess omega-6 relative to omega-3 fatty acid profile in the tissues. Then, there may be people that are driving excessive CB₁ tone by consuming large amounts of the commercially available cannabis these days.

Cannabis today has very high levels of THC and very low levels of CBD. That is not the way cannabis was 30 years ago. Back then, cannabis had more of a balance between THC and CBD. The CBD was then bred out of the plants to get higher and higher levels of THC, which creates the euphoric feeling associated with consuming cannabis.

One of our working theories is that if you have a Western, industrialized diet that is really high in omega-6 from seeds, seed oils, and meat products, and not enough omega-3 from leafy green vegetables and fish, and then you are also smoking cannabis and overactivating the CB₁ receptor, you may need to spend a little bit more energy



balancing the CB₂ receptor. And this is where CBD may play a very important role in helping to balance what we call *endocannabinoid tone*.

These are things that the natural practitioners and the dietary-supplement world are going to have to get comfortable with—how complex and how nuanced this system is. Unlike other things in the past that we have been able to reduce into simple sound-bites, we are several years away from being able to do that with both the endocannabinoid system and a very robust explanation of exactly how CBD and THC work inside of our bodies.

IMCJ: So, CBD has a mitigating effect on the euphoria stimulated by THC?

Mr Tomc: That is 100% correct. In fact, I want to give credit where credit is due. I just watched a wonderful talk at the Natural Supplements Evidence-Based Update that Scripps puts on every year. A medical doctor named Scott Shannon had a talk on natural approaches to mental health. The way he explained the dance between CBD and THC—which I thought was very interesting—suggested that maybe we should look at these things like caffeine and theanine that are both in green tea. One is a stimulant, as we know, and one is a little bit more anxiolytic.

So yes, not only is that in the medical literature, it has also been an observation that many people have made anecdotally. In the cannabis business, it is almost considered standard operating procedure that if somebody has overindulged in THC, they can take some concentrated CBD paste or high-CBD strain and it is essentially like a botanical Narcan that keeps them from being as euphoric or as high. It is fascinating that a compensatory “foot on the gas/foot on the brake” balance that was naturally occurring in the plant has been hardwired out of the plant through breeding, meaning the high THC cannabis available today bares very little resemblance to the cannabis used in antiquity. In fact, one could argue that relatively healthy people may benefit from CBD and less THC.

You might want to read the special *Newsweek* edition called “Weed Nation.” It speaks in great detail about how the cannabis from the late 1960s had very low levels of THC and had equal levels of CBD and that they had a sort of balancing effect. It was not quite as euphoric as the cannabis that people are using today under the umbrella of medical marijuana, which has 4 or 5 times the amount of THC that cannabis is naturally supposed to have.

IMCJ: With legalization beginning to reduce the stigma that is associated with cannabinoid research and bringing to light some of the findings have been buried, how robust has cannabinoid research really been?

Mr Tomc: I would not say that it is very robust yet, because we are still dealing with a schedule 1 compound. That makes it nearly impossible for researchers to do the

kind of work needed to understand types, dosages, and particular indications. That said, there are a few groups who are doing a tremendous job in fleshing out the potential benefit of cannabis and cannabis extracts.

IMCJ: Where are the hot spots in the research addressing clinical application of cannabinoids? What is showing the most promise and where is the most progress being made?

Mr Tomc: There is some potentially exciting work that we may see shortly in the area of THC and its role with cancer. But THC is a tricky one because for people that are very fragile, there is the potential of having a bad experience with THC. If they are susceptible, it may actually complicate their emotional well-being with anxiety. I am not necessarily going to call it *psychosis*, but that has certainly been an observation that people have made.

The low-hanging fruit is really in pain, inflammation, anxiety, and neuroprotection. Those are areas where there is great interest—also in posttraumatic stress disorder.

There are also 2 other areas that I think will pay enormous dividends once we can dive a little bit deeper. One of these is metabolic efficiency, if you will, or caloric utilization and nutrient partitioning. We have made the observation that regular, consistent users, specifically of highly concentrated CBD, have reported what amounts to a melting of gut adiposity—not as a direct thing that you notice right away, but slowly over time. The effect is being attributed to more efficient caloric utilization, moving you away from a fat storage machine to more of a fat-burning one. That investigation ought to be really interesting. Does it have some role in helping to activate creation of more brown or beige adipose tissue? Is that part of the mechanism of action? It has been noted that brown fat is highly thermogenic, and people certainly seem warmer when they are using concentrated CBD on a regular basis.

There is also some great opportunity in the area of mental health. We need well-controlled trials for mental health, but anecdotally it has been reported that dysregulation in the endocannabinoid system may somehow be connected to some people’s inability to let things go. So, if you think of the root of the concept of *disease*, if you cannot rest, you cannot regenerate. And if you do not sleep properly, what kind of effect does that have on your health midterm and long term?

CBD may also influence the functions of key receptors that are widely expressed and present throughout the body, specifically 5-HT_{1a}. And 5-HT_{1a} is another G protein-coupled receptor that mediates inhibitory neurotransmission. That is one of the ways that some of the SSRIs work, and CBD may have direct influence on 5-HT_{1a}. We know CBD also influences the opioid receptor, so that may be part of how it is helping with its proposed analgesic and antinociceptive mechanisms that have been reported.

I think that much more will be discovered once CBD

is officially not a schedule 1 compound and there can be free and open research. Only then can we really get to the bottom of how much CBD is required for whom.

Dosing is an area where clinicians are rightly confused, because historically people who self-medicate with cannabis have known when they have had enough for pain or for anxiety or issues with, say, sleep. They know when they have had enough because they stop using it. That role, where the patient really determines for herself or himself when they have had enough, puts this compound in a slightly different category than, “Take 2 and call me in the morning.” It is more nuanced and more complicated to dose if that is how it works.

IMCJ: At this point, I want to bring up again that you will be presenting at the American Association of Naturopathic Physicians conference coming up in the fall. Have you determined what your presentation there will be focused on?

Mr Tomc: Yes, I am going to cover the regulatory and the compliance issues. What are the conditions on the ground right now legally for cannabis?

Agricultural hemp-derived CBD and even THC are currently not unlawful according to the Controlled Substances Act, as long as the hemp is European Union-certified and lawfully imported. Few people are aware of that distinction; they consider all *Cannabis sativa* marijuana.

However *Cannabis sativa* with low levels of THC are classified as agricultural hemp. Furthermore, commercial farming and extraction of hemp is still illegal in the United States and that is why the “legal” or not unlawful hemp-derived CBD is currently all imported from Europe.

I will be talking about THC and CBD. I will also be reviewing the drugs that are currently available, so I will talk in more detail about what GWPharma is currently doing and then discussing the other drugs that have existed on the marketplace for some time.

A second speaker, Tim Ziegenfuss, PhD, the founder and chief executive officer for the Center for Applied Health Sciences, which is a leading clinical contract research organization in Ohio, will be talking in detail about the endocannabinoid system, how it works—at least how we understand how it works today—, why it is such an interesting area of research, and how it interfaces with phytocannabinoids and its respective roles in areas such as pain, inflammation, neuroprotection, anxiety, metabolic health, and dysregulation in circadian rhythm. And then, of course, we will paint a picture of future research directions that could allow us to better understand this field. That is a general overview of what we will be talking about.

For more information on the 2015 American Association of Naturopathic Physicians conference, please visit <http://www.naturopathic.org/aanp2015/>.
