



S4. Ep 3 The Endocannabinoid System and How to Affect it with or without Cannabis

Kara Ware

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Kara Ware

This is Good Medicine On The Go.

Nathan Morris

After a decades-long drug war, legal cannabis finally appeared on the horizon in the 1990s. By 1996, the State of California introduced medical marijuana cards as a method of legally obtaining therapeutic cannabis in the U.S. These cards were and still are issued to adults with the doctor's clearance for treatment of 50 different conditions, ranging from AIDS to glaucoma. Yet, is there science to support cannabis treatment for all of these disorders? Is it enough to validate therapeutics? What does the research tell us? To answer these questions and to really understand the scope of cannabis therapeutics, we have to dive deep beyond the prejudice, products, and politics, and into your cells. We have to take a look at a wide-ranging biochemical communication and regulatory system that is primary early bound in the central and peripheral nervous systems, as well as in the immune system, a system that was only discovered in the late eighties, the endocannabinoid system.

Kara Ware

In late 2021, certain restrictions were lifted. And with that, we expect a flood of new cannabis research to be published in the coming years.

Nathan Morris

In the meantime, more and more patients are consuming cannabis. I mean, just look at the statistics, either recreationally or to self-medicate. And it falls on healthcare providers to do their best with what information we do have to help patients navigate the world of cannabis safety.

Kara Ware

All right. In today's episode, we'll take a look at what research has been done, quickly review how the endocannabinoid system works and why it's important, and explore a few ways that you can support your patients' endocannabinoid systems with and without cannabis. Let's start by taking a look at the research. We might as well start at the beginning, Nathan.



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Nathan Morris

Yeah.

Kara Ware

In the 1960s, despite its classification as a Schedule I drug, the National Institutes of Health, which is the United States' federal medical research agency, actually began funding research on cannabis.

Nathan Morris

Now that's the definition of irony.

Kara Ware

Right. Because, on one hand, you've got politicians pushing anti-cannabis laws. And on the other hand, there's this federally backed medical research agency funding cannabis research.

Nathan Morris

Sounds like politics to me, Kara, as I know it.

Kara Ware

Right. A lot of the NHS' funding was going halfway across the world to Dr. Raphael Mechoulam at the Hebrew University of Jerusalem in Israel. He is known as the Godfather of Cannabis.

Nathan Morris

This partnership with Dr. Mechoulam would last 50 years. And during that time, evidence of the ECS emerged in the 1980s as researchers attempted to explain the psychotropic effects of the primary phytocannabinoid found in cannabis, delta-9, or THC, tetrahydrocannabinol. This ubiquitous system is responsible for processing endogenous and cannabis-derived exogenous cannabinoids.

Kara Ware

Whew, that was a mouthful. Okay. That's a good start though.

Nathan Morris

Yeah, it is.

Kara Ware

Studying the endocannabinoid system is one thing, but conducting clinical trials to understand the safety and therapeutic applications of cannabis is another. And up until recently, researchers in the U.S. were



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only allowed to use cannabis from a single facility based at the University of Mississippi, which was reported to have low-grade cannabis.

Nathan Morris

Yeah, Kara, I went to school in Mississippi. Let me just say, them being on the cutting edge of things like cannabis is there's another irony. That it was low grade, I don't doubt. The current research is further complicated by non-congruous forms of treatment, like different strains of cannabis, different ratios of THC and CBD, different dosages, different ways of consuming cannabis. The list goes on and on and on really. Basically, there are a lot of studies out there, but they are hard to compare since the variables between the studies are so different. Beyond this, the clinical trials that have been performed focused strictly on cannabis pharmaceuticals, which are only applicable for a small number of patients. And the research has primarily been geared towards the negative side of recreational cannabis use, like addiction and side effects, et cetera.

Kara Ware

Right. Wow, overall, given the legal restrictions and complications between the different studies, it makes interpreting this whole body of literature really challenging.

Nathan Morris

Oh my goodness, it really does. But, there is some hope. In December 2021, this last month, the DEA, Drug Enforcement Administration, released a statement saying they will approve additional American companies to produce cannabis for medical and scientific purposes so there will be greater access and hopefully to better products beyond just the University of Mississippi. This is going to be instrumental in understanding the plant's health effects and possible therapies for treating different medical conditions.

Kara Ware

In the meantime, we encourage all of us to take a look at the research for ourselves. The current research prevents us from making direct recommendations. We can't recommend a protocol, but there are still plenty of case studies and anecdotes in favor of cannabis. And we've linked some great resources in the show notes to help you get started.

Nathan Morris

Ultimately, whether or not you feel comfortable recommending cannabis, this is a personal choice. For patients whose tried everything and is still suffering, maybe what research is available now, is it good enough? I think sometimes that may be the case. Maybe not. Either way, knowing the basics of cannabis and the endocannabinoid system is important since so many patients have access to cannabis and may already be self-medicating with it. One in five are.



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Kara Ware

On that note, Nathan, let's switch gears and talk about the endocannabinoid system. This is an incredible system and can give us clues to know where and when cannabis might be useful.

Kara Ware

Despite limited research on the therapeutic applications of cannabis, we do know much about what happens to our bodies when we ingest it.

Nathan Morris

When a person ingests cannabis, it can have a variety of effects on the body. It turns out all vertebrates share something in common more than just a back bone. The highly conserved endocannabinoid system, which was actually named after the discovery of cannabis, "endo" meaning "within," and "cannabinoid," together meaning literally the inner cannabinoid system.

Kara Ware

We have a natural system for processing cannabinoids.

Nathan Morris

Yeah, exactly. I mean, evolutionarily, this has been big in all vertebrates. We've invited a colleague of ours, Dr. Kelly Heim, who will break down what we know about the ECS and how we can impact it. Kelly, why don't you introduce yourself?

Kelly Heim

My name is Kelly Heim. I am Senior Scientific Director of Genomics and Pharmacology for the Healthcare Practitioner Brands of Atrium Innovations. I got my pharmacology degree from Dartmouth Medical School. I have a doctorate in pharmacology. The reason I went into this field is because I wanted to be strategic about developing new medicines and new options to try difficult diseases and improve patient care in a way that is as exact and precise and evidence based as possible. This topic is of great interest to me because it allows us to incorporate some of the molecular data that has evolved on cannabinoids and apply them clinically.

Nathan Morris

Kelly, why is understanding the endocannabinoid system an important first step in using medicinal cannabis?

Kelly Heim

I always think about this question. If you're a clinician, why should you know about mechanisms of action? Why is that important? It's very important for a number of reasons. And one of them is you can



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better understand how different medicinal agents, therapeutic agents, could interact. You'll be able to integrate information regarding the effect of genetic polymorphisms that affect those individual molecular targets. And you'll just be better able to understand the therapeutic options that are available to you. Don't skip the mechanism of action in your self-education, on any topic that has to do with selecting a modality that's going to be best for your patient.

Kara Ware

Tell us about the system. What is it and what does it do?

Kelly Heim

The ECS is the endocannabinoid system, and this is a signaling network that regulates diverse processes in the central nervous system, as well as in peripheral organs and the immune system. It plays really important roles in regulating all kinds of things like relaxation, pleasure, memory, thinking, concentration, awareness of time, appetite, sensory processing, and even inflammation. It consists of chemical messengers called endogenous cannabinoids or endocannabinoids and the receptors that they activate, along with various enzymes that control the synthesis and degradation of these compounds. If you want to explain the ECS to a patient, or if you want to understand it in simpler terms, think about a volume knob on your radio, how you turn it up or turn it down. That's what the ECS does. It's like a volume knob that can amplify or diminish a chemical signal.

Kelly Heim

That signal could be neurotransmission. It could be inflammation, it could be something else that could potentially be out of control at a given moment. And when that cellular information exchange gets out of hand or thrown off balance, the ECS steps in and helps to restore and maintain homeostasis. It essentially is there to ensure that cells communicate effectively, but not excessively. When you think about the brain, the central nervous system, the ECS is engaged when a neuron or cell gets overly excited by a neurotransmitter or overly inhibited by a neurotransmitter. And that excess will stimulate specialized enzymes that create endocannabinoids on the spot, and they act a damp in that excessive input. We're talking about fine tuning signals to maintain balance or homeostasis.

Kara Ware

This system seems to have a multifaceted role in regulating our bodies by maintaining an ongoing balance.

Nathan Morris

Exactly. It's kind of a dance between the endocannabinoids, anandamide and 2-AG, the enzymes that regulate their activity, and the receptors that they bind to. There are many receptors that play a role in ECS, but the main ones are CB1 and CB2. CB1 is found primarily in the central nervous system and helps



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regulate neurotransmitter activity. CB2 is found in the peripheral tissues, organs, and immune cells, and is going to play a stronger role in systemic activity like controlling inflammatory mediators.

Kara Ware

I love the visualization as the volume knob in our bodies. You both did a great job explaining this complex system in a comprehensible way. What else do we know about the ECS besides its major components?

Nathan Morris

The ECS is already helping you and you might not even know it. When you exercise, you're getting a hit from the endocannabinoid system. You ever need help with sleep, anxiety, or pain? The ECS naturally plays a role in these processes.

Kara Ware

Wow. It's so interesting to get to know this new system and how it's related to our patients' top objectives and to understand this is how our body adapts to our environment every day.

Nathan Morris

Yeah, Kara, it's pretty amazing. Really, if you think about it, the ECS is one of the largest receptor systems in the body and it's one of the master regulators of homeostasis in the human body. Just think about that. One of the master regulators of homeostasis. Even though it has only been discovered in the 1980s, it has such a huge impact on your wellbeing.

Kara Ware

Okay, so now that we know about the ECS, let's get into the fun stuff. How to affect this system? Coming up, we'll cover three ways of influencing the endocannabinoid system. Phytocannabinoids, pharmaceuticals, and non-cannabis interventions.

Nathan Morris

Well, the obvious answer in my opinion is cannabis, which contains dozen of phyto or plant-derived cannabinoids. The two main cannabinoids, I'm sure you heard of, are THC and CBD. Maybe.

Kara Ware

Oh yeah, maybe. THC and CBD, they're definitely the celebrities of the phytocannabinoid world. But, there are over 150 phytocannabinoids that have yet to be fully researched. And so, Kelly, will you talk with us about these celebrity compounds first that we do have research on and the difference between them?



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Kelly Heim

Cannabis contains many different active substances, including phytocannabinoids. There are over 100 different phytocannabinoids that have been isolated from cannabis, but the two that are most well-known and widely used are THC, or delta-9-tetrahydrocannabinol, and CBD, or cannabidiol. THC is very different from CBD. Now, CBD and THC look very similar on paper. Their two-dimensional structures are very, very similar, but if you look at them in a 3D space, which I definitely have because this is the nerdy stuff I do in my spare time, they look very different, and they're not able to engage the same molecular targets. CBD is not able to bind to that same site on the CB1 receptor. That's why CBD has no psychoactive properties. It's not able to create euphoria. It's not able to impair cognition. It will not create a lot of the adverse effects of THC. However, it's not going to have the same therapeutic properties and indications.

Kelly Heim

The pros, THC does have approved medical indications, such as nausea, loss of appetite. The most accepted medical application of THC is as an appetite stimulant and as an antiemetic. I don't think anybody would disagree. That's pretty much consensus knowledge. THC should be considered I think for those unique circumstances. THC can also have a sedative effect, it can sedate. It can create a relaxed state. THC affects the hippocampus and the orbital frontal cortex that allow us to remember and focus on things. If you need to remember something and focus on something, THC is going to inhibit your ability to do that. THC also interferes with multiple cognitive domains. You should never operate machinery if you're on THC. It will also disrupt your balance, coordination, reaction time, could cause dizziness. There are some dangers as associated with that. The cons of THC really are the side effects and legal restrictions that applies to many states.

Kara Ware

Okay. What I'm hearing is THC is psychoactive and helps with relaxation, nausea, and loss of appetite by acting on CB1 receptors, which are primarily located in the central nervous system and the gut. But, of course, there are some side effects, which are important to consider if recommending a product with THC. Let's dive into CBD now. Kelly, what is important for our audience to understand about the effects of CBD?

Kelly Heim

One of the effects that's been identified by several authors is that CBD inhibits an enzyme that breaks down your endocannabinoids. In doing so, it can stabilize levels of your endocannabinoids and help them work better. That enzyme is called fatty acid amide hydrolase, or FAAH. The problem with some of the evidence on that is that you need a high dose of CBD in order to get that effect. And it's probably not happening in a clinical environment, probably not able to get the dose that you would need. Several research papers have explored other mechanisms of action. And currently, the consensus is that CBD



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activates a serotonin receptor, serotonin type 1A receptors. That explains why it can have a calming effect on neurons.

Kelly Heim

As far as indications for CBD, again, I would say, calming the central nervous system. Relaxation would be number one, depending on who you ask. There are a lot of other reasons people are using it, but I think that probably is the most appropriate as the leading indication just based on what I know, but probably others will pop up in the future as more research unfolds. As far as CBD, the pros would be, well, it's widely available. It's much better tolerated, doesn't cause cognitive impairment. Really, it doesn't have the same adverse effects as THC. In fact, it's extremely safe at the doses that are available. The cons would be it's no substitute for the qualified medical uses of THC that I mentioned. The gastrointestinal and appetite-stimulating indications would not apply for CBD. You also really want to look at the dose on the labels. A lot of CBD products out there have a very low dose.

You want to look for something that's at least 20 milligrams. And I think that's just the number one thing you want to look for. CBD formulations will vary considerably in terms of the dosage and the bioavailability.

Kara Ware

CBD activates serotonin receptors. That explains why it can have a calming effect. Something that wasn't mentioned was a potential for CBD to have anti-inflammatory effects, which have been reported in a couple animal studies.

Nathan Morris

Now, of course, cannabis is made up of more than just these two cannabinoids. As Kara said, there's almost 150 phytocannabinoids and counting associated with cannabis, the plant. And when you take in the whole plant, there are a lot of other beneficial compounds.

Kara Ware

Our audience might have heard about terpenes before, but in case they haven't, Kelly, would you mind touching on why these are such interesting components of cannabis?

Kelly Heim

Terpenes are small lipophilic molecules that are dispersed throughout the plant kingdom, particularly in herbs and spices. These are the compounds that contribute to the flavor and the pungency and the unique sensory properties of culinary herbs and spices, including pepper and other plants that you probably have in your spice cabinet. Terpenes are very bioavailable to the central nervous system. One of the terpenes that has gained a lot of attention is beta-caryophyllene. Beta-caryophyllene is a CB2 receptor agonist. The CB2 receptors are located on the surface of immune cells that would normally



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release inflammatory mediators. And by activating the CB2 receptor, you're turning down a different volume knob, the volume knob that would control the release of inflammatory cytokines.

Kelly Heim

If you're dealing with an immune cell that's overactive, secreting these compounds, these chemical mediators in excess, then endocannabinoids act to turn that down by activating the CB2 receptor, and beta-caryophyllene can activate the exact same receptor with a high degree of cell activity and affinity. We're not just talking about these phytocannabinoids, CBD, and THC. We're talking about a diverse array of terpenes that occur not only in hemp but elsewhere in medicinal plants and in the foods that you eat. That's an interesting area of research that has more to do with inflammation and peripheral target sites of endocannabinoids.

Kara Ware

Kelly, I've seen many articles and media mention the entourage effect and how it may be more beneficial to consume cannabis in more raw forms to get the benefits of the terpenes and phytocannabinoids together. Is there evidence of this?

Kelly Heim

The entourage effect was introduced in 1999 as a proposed mechanism by which the constituents of cannabis act synergistically with THC to modulate the overall psychoactive effects of the plant. It has since had multiple meanings. I think originally the intent was to talk about the synergy and cooperativity of your endogenous cannabinoids. Today, if you ask somebody about the entourage effect, it's used to describe the synergy, the interactions, that favor, the superior effect of a full spectrum extract or a whole plant compared to an isolated constituent. This has been thematic throughout conversations of about botanical medicine from the beginning. This is not a new conversation. It seems to have gained a lot of popularity when talking about different hemp products and which one is best because it's just so confusing. It's nice to have some kind of a principle to unite everyone's confusion and to justify the selection of a more complex extract or whole extract or product.

Kelly Heim

It has come under criticism. In recent years, there was a 2020 review that found no evidence of an entourage effect and concluded that the phrase itself is unfounded. I caution clinicians and patients to avoid the assumption that a whole plant or a full spectrum extract is really better simply because it contains a longer list of phytocannabinoids and terpenes. The only exception would be if there's actual data that shows a clinical response being superior for a full spectrum extract compared to an isolated compound. Don't make assumptions. This is something that I think that people are tempted to do. Always look for clinical data whenever possible, which may or may not be available. This is an area where there's just not a lot of comparative clinical data to say that one product is better than another. Be conservative about how you interpret the entourage effect.



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Nathan Morris

I do see it clinically, and CBD with THC gives you a totally different effect than if you just did THC alone, or if you did CBD alone. And looking at a whole plant with over a hundred plus compound, it kind of goes against mother nature to say, "Oh, we can just isolate this one compound and we're going to get the same effect as if we do the whole plant." It's like I've been studying turmeric, and there's a lot of things we pull out sometimes and we get good effect just with curcuminoid, but I think there's a lot of other things there that are very beneficial and I think the research is starting to show that. What's interesting is we can look at what happens when you isolate a certain compound from cannabis and that's with the pharmaceuticals, and sometimes you can have rather severe side effects when you don't have those counterbalances that come with what I call the entourage effect.

Nathan Morris

There are a handful FDA-approved prescription medications that are derived from cannabis or made from synthetic cannabinoids. As with all pharmaceuticals, you must get a prescription from your doctor as an additional therapeutic for very specific disorders.

Kara Ware

Right. After spending decades enacting laws against cannabis, the FDA is the one to approve medications containing it. For example, Epidiolex, which contains a purified form of CBD, derived from cannabis. This was approved for the treatment of two rare and severe forms of epilepsy.

Nathan Morris

And there's Marinol and Syndros, which contain dronabinol. You've got to love my pronunciation, Kara. I'm from Louisiana so we have to give me some leeway here, audience. Which is a synthetic THC. And Cesamet, which contains nabilone. They're just killing me today. Nabilone is a synthetic substance similar to THC. It's also approved by the FDA. Dronabinol and nabilone are used to treat nausea and vomiting caused by cancer chemotherapy. Dronabinol is also used to treat loss of appetite and weight loss in people with HIV and AIDS.

Kara Ware

These pharmaceuticals are typically used in conjunction with other treatments and often contain lab-created highly concentrated THC or CBD, which may have more serious negative effects on patients.

Nathan Morris

That's very true, and I alluded to it earlier. Prescription cannabinoid products have a narrow scope of use and are not considered first line therapies, including the FDA-approved prescription cannabis products. Because these products are purified and or synthetic, these products don't have the natural side effects or synergy seen in natural forms. Meaning, clinicians are encouraged to try something else



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before using these products. You may not use these products regularly in your practice but there are options, sometimes life changing for a very small group of patients with specific needs.

Kara Ware

We all know that everything has potential risks, prescriptions and plant medicine. It's always a good idea before considering the pharmaceuticals to read the package insert and even provide it to your patients. I think that'd be a good practice to be consistent with.

Nathan Morris

Beyond phytocannabinoid-derived pharmaceuticals, there are other drugs that influence ECS like antidepressants, NSAIDs, or opiates.

Kara Ware

Right, Nathan. The ECS plays a role in so many facets of our health and it's important to know how we treat our bodies of course can influence how this system reacts. Therefore, the last way we're going to talk about today is to affect the endocannabinoid system through non-cannabis-derived interventions.

Nathan Morris

Given how widespread and ubiquitous the endocannabinoid system is in the body, it's no surprise that many lifestyle factors and therapeutic interventions can affect it. Things like diet, exercise, and then there're supplements such as omega-3s and probiotics, as well as things like massage, acupuncture, and even caffeine intake. These all affect the endocannabinoid system. Kelly had some thoughts on this as well.

Kelly Heim

You may have experienced that runner's high or that great feeling that you get after a good workout. And that is due in part to the stimulation of endocannabinoids. That's an easy thing to do, that's one thing we already know is good for us. And there are probably other lifestyle measures that intersect with the endocannabinoids system. Things that we already know are good for us may very well in part modify endocannabinoid signaling in a therapeutic way, but more research is needed to define exactly how that happens. Currently, the research is focusing on not only phytocannabinoids, which are plant-derived cannabinoid compounds, but other substances that have nothing to do with cannabinoids, like combining fatty acids and amines to create N-acyl amides. These are substances that there are no structural similarity really to cannabidiol or THC, but they are very effective in modulating endocannabinoid tone.



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Kelly Heim

The combinatorial diversity when you think about all the amides and amino acids and all the lipids we have in nature, we could create a huge palette of new cannabinoid-modifying compounds. Also, if you look at natural compounds like altheine and compounds from Echinacea called algamins... Algamins are fat-soluble compounds that have been known for many years to support endocannabinoid signaling. Plants have a lot of compounds that could potentially modify the endocannabinoid system in a way that would make them useful in clinical practice. But, the research is definitely premature at the current moment to make specific recommendations.

Kara Ware

Slowly but surely we have started recovering from the oppressive past and new evidence is rapidly emerging on studies investigating clinical applications for cannabis. We've talked today about how the science is new but full of promise, and that the FDA has approved a few pharmaceuticals for clinical use.

Nathan Morris

Dr. Kelly Heim did a wonderful job of connecting the dots, what the endocannabinoid system is and why it's important to understand this powerful system before recommending phytocannabinoids and other compounds that affect it.

Kara Ware

The ECS has that volume knob, our master regulatory system in how we adapt to the environment. So much impact for a system that was only discovered 30 years ago.

Nathan Morris

Yeah, hard to believe.

Kara Ware

Whew. We've linked a few key studies in our show notes that can help guide you on starting your journey and to researching this topic.

Nathan Morris

Kara, we're ready to start using cannabis? Is that what you...

Kara Ware

Yeah, let's just jump in. Ready, fire, aim.

Nathan Morris

Yeah...



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Kara Ware

Not quite. It is important that we not just focus on the promise of cannabis but also the potential risks of using therapeutic cannabis, so that we can provide a fully-informed clinical approach.

Nathan Morris

Tune into our next episode that jumps into answering, "Can cannabis cause harm," which is a great question, I think. As providers, we need to know that. And what are the legalities of cannabis medicine?

Kara Ware

Right. The goal is to offer complete informed consent to your patient, and there is a lot to know.

Nathan Morris

It's safe to say that it's the early days for cannabis, but that doesn't mean it can't have a place in your toolbox. Catch you next week.

Kara Ware

Thank you for listening as Nathan and I re-imagined the functional medicine journey as we explore how to include cannabis in our functional medicine toolbox. I would like to thank our writing team, Kelsey Stafstrom, Paul Larkin, and Isabel Manjeau, and our audio engineer, Isadore Neavaz. If you would like to support this podcast, please follow us and visit karawarecoaching.com. That's K-A-R-A-W-A-R-E.coaching.com for cannabis resources and unedited interviews. Plus, more podcast seasons, minisodes, nutrigenomics case study events, and business coaching.