Debates and issues pertaining to the entourage effect

David A Dawson *

Department of Psychology, Northcentral University, San Diego, California, USA.

GSC Biological and Pharmaceutical Sciences, 2022, 20(02), 180–183

Publication history: Received on 15 July 2022; revised on 19 August 2022; accepted on 21 August 2022

Article DOI: https://doi.org/10.30574/gscbps.2022.20.2.0327

Abstract

The following disquisition investigates interpretations, insights, and inconsistencies causing conflicts, controversies, and consternation within the segment of the scientific community that studies the viability of treating physiological and psychological conditions through the administration of botanic cannabinoids. The intrinsic constructs and theories involved in this aspect of scientific inquiry are complex and convoluted, with deep-rooted biases dependent on the paradigm to which the researcher subscribes. This paper aims to examine two constructs of controversy, each related to competing paradigms inherent within the study of biomolecular psychology.

Keywords: Entourage Effect; Endocannabinoid; Phytocannabinoid; Terpene; Receptor

1. Introduction

The half-century prohibition of research in the United States on the medicinal properties of biological cannabinoids has forced American cannabinoid scientists to analyze and develop theories based on studies conducted in other countries yet ironically funded by the National Institutes of Health (NIH). NIH is a part of the U.S. Department of Health and Human Services and is considered America's medical research agency. The agency is credited with making important discoveries that improve health and save lives.

Theories are inseparable from clinical observations, and the inability to conduct practical research in their country of origin has resulted in American cannabinoid scientists producing tens of thousands of review articles espousing theoretical explanations for the results of clinical trials funded by the United States but in which they were prohibited from being involved. Arguably, the two most important theories related to cannabinoid-based therapies are the entourage effect theory and the theory of endocannabinoid deficiencies. Each reinforces the other, and both support a comprehensive theory of phytocannabinoid supplementation for endocannabinoid deficiency disorders.

2. Material and methods

2.1. Theories are constructed on Clinical Observations

The most prolific cannabinoid researcher is Dr. Raphael Mechoulam, a biochemist that NIH funded at the Hebrew University of Jerusalem. Mechoulam was the first researcher to propose the entourage effect theory when he discovered that 2-linoleoylglycerol, 2-oleoylglycerol, and 2-palmitoylglycerol do not bind to cannabinoid receptors but enhance the binding potentiation of 2-arachidonoylglycerol. This observation inspired Mechoulam to propose that the congeners synergistically enhance the endocannabinoid's binding potential to the primary cannabinoid receptors, theoretically through inhibition of 2-arachidonoylglycerol degradation [1].
2.2. The Controversy of the Entourage Effect

Whether the topic is politics, pharmacology, applied therapeutics, or botanical taxonomy, cannabinoid science tends to curry controversy in every sphere of its influence. However, because of difficulties in distinguishing one cannabis cultivar from another based on factors such as plant height and leaflet width and the fact that all cannabis types are eminently capable of crossbreeding to produce fertile progeny, the only reasonable solution is to classify them by their biochemical/pharmacological characteristics and refer to forms of cannabis as “chemovars” or chemical varieties [2]. These chemovars are analogous to phytochemical factories producing terpenes and cannabinoids, many with well-documented medicinal properties [3].

Perhaps the most controversial construct involving cannabinoid-based therapies is the entourage effect, the idea that constituents in cannabis chemovars act synergistically to magnify or mitigate the supplement’s effects. Ethan Russo, a neurologist and former director of research and development at the International Cannabis and Cannabinoids Institute in Prague, extended this concept to the theory of endocannabinoid deficiencies, postulating that chemicals in the cannabis plant could enhance, heighten, or mitigate the psychoactive and therapeutic effects of THC. He contended that CBD works to enhance THC’s therapeutic effects [4]. As evidence, he cited a 2010 clinical trial of Sativex, a botanical compound comprised of THC and CBD, to treat neuropathic pain in people with multiple sclerosis [5]. The study consisted of 177 participants and had three arms. The first group received a placebo, the second was given a compound containing high concentrations of THC, and the final group was treated with Sativex. Participants were asked to score their pain throughout the two-week clinical trial and state at the end how much their pain had lessened, if at all. A reduction in pain of 30% or more was considered clinically significant. Approximately 40% of the people treated with Sativex reported this level of pain relief, almost twice as many as those that received the placebo or THC alone.

Another study supporting the existence of an entourage effect is a 2018 meta-analysis involving 670 people with treatment-resistant epilepsy and given either purified CBD or full-spectrum CBD-rich cannabis extracts. 71% of those in the group of participants scored a reduction in pain of 30% or more; almost twice as many as those that received the placebo or THC alone [6].

The entourage effect theory was seized upon by cannabis suppliers and is promoted relentlessly as a marketing tool for products containing a full spectrum of phytocannabinoids and terpenes. As with many scientific theories, the entourage effect is not universally accepted within the scientific community, and acceptance of the construct appears to be correlated to research funding sources. The pharmaceutical industry is mired in a one-molecule approach to medicine and has funded studies that assert the synergizing components are not inherently pharmacologically active and suggest the construct is merely a marketing ploy by marijuana companies peddling illicit drugs with no federally accepted medicinal components [7]. Scientists funded by cannabis companies also exhibit some bias in their publications, and objective researchers must constantly scrutinize the motivations behind how and why scientific knowledge is constructed.

While the bias in the Cogan review is evident, other researchers deny the existence of the entourage effect with considerably more acularity. Recently, a group of researchers replicated the experiment in which Mechoulam and his colleagues studied the endocannabinoid 2-arachidonoylglycerol (2-AG), which binds to primary cannabinoid receptors [8]. As previously discussed, the Mechoulam group discovered that in mice’s brain, spleen, and gut, 2-AG is characteristically found together with two other compounds: 2-linoleoylglycerol and 2-palmitoyleglycerol. Unable to activate the primary CB1 and CB2 receptors themselves, these two molecules facilitate 2-AG’s potential to bind to the receptors and increase effects such as analgesia in the animals [9].

The study, conducted in 2016, replicated the Mechoulam experiment, examining the unknown but closely related lipid species, with fatty acids of different lengths and saturation: 2-oleoylglycerol, 2-linoleoylglycerol, and 2-palmitoyleglycerol. This replication utilized cutting-edge instrumentation to examine whether these lipid progenitors are degraded by the same enzymes as 2AG, thereby competing with 2-AG for breakdown. If this competition exists, the result would be an enhancement of 2-AG concentrations and a prolongation of 2-AG signaling, sans an entourage effect [10]. To test this proposition, the researchers replicated the experiment conducted by Mechoulam using instrumentation to which Mechoulam had no access, attempting to dispute whether the progenitors he and his group didn’t know existed act in a manner inconsistent with the role of entourage compounds in these diverse models of 2-AG signaling. They had access to better cell lines than the immortalized cell lines the Mechoulam group used and did not fully recapitulate endogenous cannabinoid signaling. Instead, they utilized autaptic hippocampal neurons, a model system that possesses the necessary mechanism to suppress activation.
Using a superior experimental design, advanced technology, and better cell lines, the results of the replication of the Mechoulam experiment showed that 2-oleoylglycerol, 2-linoleoylglycerol, and 2-palmitoylglycerol do not behave in a manner consistent with entourage compounds. Instead, all compounds, but most notably 2-oleoylglycerol, acted as antagonists. 2-palmitoylglycerol very slightly antagonized the CB2 receptors, while 2-oleoylglycerol demonstrated the most significant antagonistic effect in neurons and weakly antagonized the CB1 receptors.

2.3. Evaluation of Study

While this replication study was well designed and analyzed fatty acids of which the Mechoulam group was unaware and incorporated instrumentation and cell lines to which they had no access, the results as reported fail to negate the fact that endocannabinoid system compounds act synergically to modulate the effects of the endocannabinoids on the primary and secondary cannabinoid receptors. The fact that 2-oleoylglycerol and palmitoylglycerol act as antagonists indicates they mitigate the effects of 2AG and is indicative of an entourage effect. Additionally, as with many other studies, the researchers point out that 2-oleoylglycerol, 2-linoleoylglycerol, and 2-palmitoylglycerol may independently activate the GP55 receptors, with no entourage effect involved. There are multiple claims in the literature that the GP55 receptors are cannabinoid receptors because most biologic and synthetic cannabinoid molecules activate them [11, 12, 13, 14]. Respect for this research wanes because there seemingly are few molecules that do not turn the GP55 receptors on [15]. Furthermore, even if no entourage effect existed in this instance, it would not eliminate its existence in other instances.

Of the 57 articles in the Medline database that mention the entourage effect, three (5%) discount its existence. The pharmaceutical industry funded the two previously described, which attempt to discount the theory entirely. The Lambert Initiative for Cannabinoid Therapeutics funded the third. Entitled Terpenoids Commonly Found in Cannabis sativa Do Not Modulate the Actions of Phyto cannabinoids or Endocannabinoids on TRPA1 and TRPV1 Channels [16], this study assessed the effects of α-pinene, β-pinene, β-caryophyllene, linalool, limonene, β-myrcene, and α-humulene on the transient receptor potential ankyrin 1 (TRPA1) and transient receptor potential vanilloid receptors (TRPV1) and whether they modulate endocannabinoid or phytocannabinoid agonists on these receptors. The authors admit the entourage effect exists in the interplay between the phytocannabinoids cannabidiol and Δ⁹-Tetrahydrocannabinol and examined whether the terpenoids modulate the effects of phytocannabinoids at TRPA1 and 1 TRPV1 channels.

3. Results and discussion

The terpenes analyzed failed to affect the actions of Δ⁹-THC on the TRPV1 and TRPA1 receptors. Even so, these results do nothing to negate the entourage effect of certain terpenes. It has been well established that myrcene synergizes the other terpenes’ antibiotic properties and changes the permeability of the cell membranes to allow for better absorption of cannabinoids into the brain [17]. Additionally, menthol is widely used as a permeability enhancer in clinical medicine due to its high efficiency and relative safety [18]. The money the pharmaceutical industry pays scientists to publish studies disputing the entourage effect does nothing to change the fact that it is a natural phenomenon.

4. Conclusion

Perhaps the most controversial construct involving botanic cannabinoid medicines is the idea that constituents in cannabis chemovars act synergically to magnify or mitigate the supplement’s effects. The entourage effect theory has been seized upon by cannabis suppliers and is promoted relentlessly as a marketing tool for products containing a full spectrum of phytocannabinoids and terpenes. As with many scientific theories, the entourage effect is not universally accepted within the scientific community, and acceptance of the construct appears to be correlated to research funding sources. The pharmaceutical industry is mired in a one-molecule approach to medicine and has funded studies that assert the synergizing components are not inherently pharmacologically active, suggesting the construct is merely a marketing ploy by marijuana companies peddling illicit drugs with no federally accepted medicinal components. This article summarizes the research acknowledging and disputing the existence of the entourage effect, concluding that despite the significant bias inherent in many published studies pertaining to its existence, disputing it does nothing to change the fact that it is a natural phenomenon that lends to the efficacy of nutraceutical medicines.

Compliance with ethical standards

Acknowledgments

Gratitude, respect, and appreciation are extended to Spectral Analytics and the CannaCare Foundation for their support in the creation of this work.
References


