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Psychosocial and Biological Aspects of Synthetic and Natural FAAH Inhibitors

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Abstract

Molecular engineers are studying FAAH as a target for pharmaceuticals as controlling levels of FAAH may produce some of the same health effects that excite clinicians about the potential for phytocannabinoid-based medicines. Synthetic cannabinoids work by flooding the system with molecules structurally similar to THC and other phytocannabinoids. Medicines that inhibit the body's production of FAAH are theorized to have a similar effect by maximizing the concentration of deficient endocannabinoids in the nervous system. Technological limitations coupled with a suppression of research of biologic cannabinoids at many major research universities have limited our understanding of the endocannabinoid system. Questions still need to be answered to provide a comprehensive comparison of biologic with synthetic FAAH inhibitors. Advancement and research aimed at understanding of endogenous and exogenous cannabinoids, and particularly the medicinal properties of the Trans-Δ⁹-Tetrahydrocannabinol (THC) molecule and its endocannabinoid equivalent anandamide are hindered by prohibitive restrictions resulting from the Food and Drug Administration (FDA), Drug Enforcement Administration (DEA), National Institute of Health (NIH), and the National Institute on Drug Abuse (NIDA). The mission statements of each of these entities effectively integrate to ensure research and utilization of the medicinal properties of THC will be nearly impossible to attain

Keywords: FAAH inhibitors, Endocannabinoid System, Endocannabinoids, Phytocannabinoids, Anandamide, Pharmaceuticals, Nutraceuticals, Biochanin A.

Abbreviations: FDA-Food and Drug Administration, DEA-Drug Enforcement Administration, NIH-National Institute of Health, NIDA-National Institute on Drug Abuse, THC-Tetrahydrocannabinol, FAAH-Fatty Acid Amide Hydrolase.

Introduction

Analyzing the advantages of pharmaceutical as opposed to nutraceutical approaches towards maintaining health from a biopsychological perspective tends to become convoluted, particularly with respect to FAAH inhibitors. This topic pertains to every age group, but typically manifests itself most dramatically at the age when individuals begin to stop producing appropriate levels of N-arachidonoyl ethanolamine (Anandamide) and 2-Arachidonoylglycerol (2-AG). Because of individual differences, and varying degrees of exposure to environments which hasten endocannabinoid depletion, age of onset varies but usually expresses itself most dramatically around the age of onset of arthritis, although various ailments and environmental circumstances can also cause deficiencies in these and other endocannabinoids.

All humans possess a measurable endocannabinoid tone reflecting levels of Anandamide (AEA) and 2-arachidonoylglycerol (2-AG). These have been designated as centrally acting endocannabinoids, and their decreased concentration shows a significant correlation to the development of lowered pain threshold, along with derangements. Autism, ADHD, Parkinson's disease, Alzheimer's disease, Crohn's Disease, diabetes, migraines, fibromyalgia, post-partum depression, muscular dystrophy, multiple sclerosis, Polyneuropathy, Post Traumatic Stress Disorder, and sleep disorders have all been implicated in studies as being caused by deficiencies of various endocannabinoids [1-15].

Endocannabinoid deficiencies can also arise due to genetic or congenital reasons or are acquired due to inter-current injury or disease, which consequently produce characteristic pathophysiological syndromes with symptomatology. Currently, competing approaches are attempting to emerge as the accepted technique for treating these endocannabinoid deficiency disorders. Each has advantages and disadvantages, both biological and psychosocial. This disquisition is designed to analyze each from a bio-psychological perspective.

Psychosocial Aspects of Pharmaceutical and Nutraceutical Approaches to Healthcare

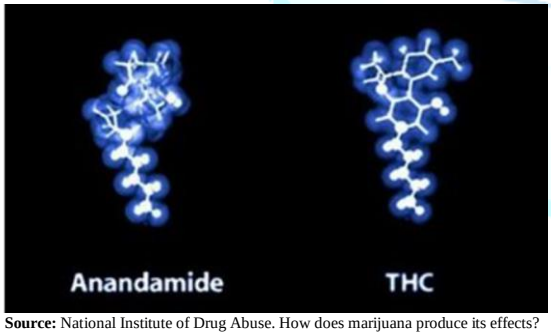
Pharmaceutical and nutraceutical approaches to treating endocannabinoid deficiency disorders compete in remarkable ways, with the former having the advantage of being able to claim FDA approval. Since its inception, people have been conditioned to believe "FDA approved" means "safe," although this perception is becoming questioned as adverse effects of FDA approved medications are increasingly exposed. The latter has the advantage of being natural, providing it some biomolecular superiority. Pharmaceuticals have the disadvantage of side-effects, often resulting from the body's inability to degrade the synthetic molecules of which they are composed.

Because they are natural, nutraceuticals have the disadvantage of being unpatentable and therefore cannot be considered for FDA approval.
While the concepts discussed in this paper relate to all forms of endocannabinoid deficiency disorders, only the deficiency of anandamide will be discussed. Due to ongoing bias against Trans-Δ⁹-Tetrahydrocannabinol (THC), phytocannabinoid supplementation for this endocannabinoid deficiency is often eliminated as a nutraceutical approach due to its potential of producing dopamine in amounts of concern to the National Institute of Health (NIH), the National Institute of Drug Abuse (NIDA), and the Drug Enforcement Administration (DEA).

The unstated and somewhat murky mandate from each of these bureaucratic entities is that researchers devise a method of increasing N-arachidonoyl ethanolamide (anandamide) levels sans the Trans-Δ⁹-Tetrahydrocannabinol molecule. THC has been excluded from the 2016 Farm Bill which classified all other phytocannabinoids as agricultural products, thereby legalizing research of their potential medicinal properties provided they are derived from varieties of Cannabis sativa that contain less than 0.3% THC. THC is the most researched of all the phytocannabinoids throughout the world and its medicinal applications are well-documented, yet the war on the cannabis plant in the United States is now focused against this individual phytocannabinoid. NIDA justifies this war because its ingestion activates the release of dopamine. Methods of activating dopamine must be legal and socially acceptable. These methods include religion, jogging, shopping, gambling, video games, and the ingestion of alcohol, nicotine, and pharmaceutical medications [16].

Anandamid and Trans-Δ⁹-Tetrahydrocannabinol

On June 25th, 2018, the National Institute of Drug Abuse published on their website their acknowledgment that the phytocannabinoid equivalent of the endocannabinoid anandamide is Trans-Δ⁹-tetrahydrocannabinol. While this was not an actual study, the acknowledgment is a significant step towards the implementation of a complementary alternative medicine approach in the United States because it indicates an acceptance of multiple research studies which America funded, but rejected consistently for well over five decades [17] **(Figure 1).**



Source: National Institute of Drug Abuse. How does marijuana produce its effects?
Figure 1: Anandamid and Trans-Δ⁹-Tetrahydrocannabinol.

Anandamide is the body's natural THC molecule possessing multiple medicinal properties, particularly an ability to relieve neuropathic pain [18]. Inhibition of FAAH increases endocannabinoid concentrations in both rats and humans providing therapeutic benefits for virtually every form of endocannabinoid deficiency disorder [19,20]. Molecular engineers are studying FAAH as a target for pharmaceuticals because controlling levels of FAAH may produce some of the same health effects that excite clinicians about the potential for phytocannabinoid-based medicines. Synthetic cannabinoids work by flooding the system with molecules structurally similar to THC and other phytocannabinoids. Medicines that inhibit the body's production of FAAH are theorized to have a similar effect by maximizing the concentration of deficient endocannabinoids in the nervous system. Put simply, if the deficiency is in Anandamide, reduced FAAH results in more Anandamide availability. While ingestion of phytocannabinoids increases the number of cannabinoid transmitters artificially through the addition of THC, the molecule produces dopamine in a federally unacceptable way.

Adverse Effects of Synthetic FAAH Inhibitors

Increasing the concentration of endocannabinoids by inhibiting FAAH and other catabolic enzymes, rather than administering exogenous agents is theorized to reduce cannabinoid-like adverse events attributed to intromission of phytocannabinoids [21]. Synthetic FAAH inhibitors exhibit neurological side effects not manifested by the biologic, including impairment of cognition and motor functions and a predisposition to psychoses, notably when these agents are used for long-term treatment [22].

The development of potent and safe synthetic FAAH inhibitors has been hindered by their deleterious side effects [23]. On July 9, 2015, Biotrial, a Contract Research Organization began human phase testing of the synthetic FAAH inhibitor BIA 10-2474 for the manufacturer by recruiting 128 healthy volunteers, both men and women aged 18 to 55. The study employed a three-stage design with 90 of the volunteers receiving the drug during the first two stages of the trial, with no serious adverse events reported. Participants of the study were asked to stay at Biotrial's facility for two weeks, during which time they would take the drug for ten days and undergo tests.

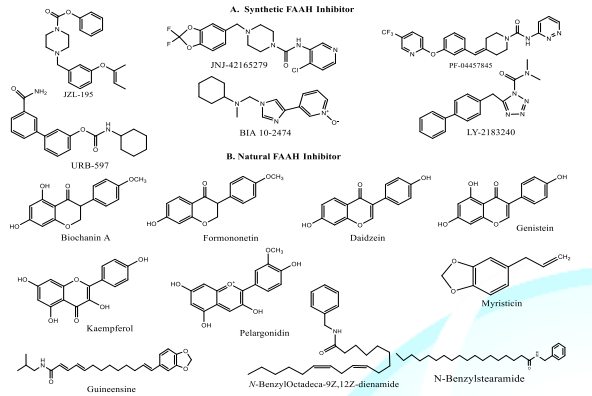
In the third stage of the trial evaluating multiple doses, six male volunteers received doses by mouth, starting on 7 January 2016. The first volunteer was hospitalized on January 10, became brain dead, and died on January 17. The other five men in the same dosage group were also hospitalized from January 10 through January 13, four of them suffering injuries, including deep hemorrhagic and necrotic lesions seen on brain MRI. Professor Pierre-Gilles Edan, a neurologist at the University of Rennes Hospital Center, stated in a press conference that three of the four men were displaying neurological symptoms severe enough to create a "clinical picture to fear that even in the best situation there will be an irreversible handicap." The experiment was discontinued on January 11, 2016 [24]. Many questions remain unanswered, including the biomolecular mechanism causing the participants' injuries. Magnetic-resonance-imaging scans revealed dying and bleeding tissue deep in the brain.

The devastating result of this clinical trial led to a scramble of scientists proposing various explanations as to the cause of the deadly side-effect resulting from the synthetic FAAH inhibitor. It has been suggested that the adverse events may come from its binding to unidentified off-targets. However, few methods exist to predict cellular off-target effects resulting from the drug binding to biological assemblies, and their associations with diseases [25]. Owing to these limitations, it is still unclear what the off-targets of FAAH inhibitors are, and how the off-target affects the system-level response [26].

Degradation of Synthetic and Biologic FAAH inhibitors

FAAH inhibitors are designed to remove fatty acid amide hydrolase proportionally, thereby increasing the concentration of anandamide naturally produced by the body. While synthetic FAAH inhibitors have been demonstrated to do this, we now know enough about both the endocannabinoid system and biomolecular psychology to theorize about the mechanism by which synthetic compounds cause neurological damage [27]. The adverse effects are likely not a byproduct of FAAH-inhibition directly, but rather the result of biologic enzymes being incapable of effectively degrading them. Biologic

FAAH inhibitors demonstrate significant differences in their molecular structures than their synthetic counterparts, and the differences in the molecular structures may account for differences in the safety profiles between the synthetic and the biologic. These differences could be related to the time it takes the FAAH inhibitors to degrade. Information is lacking about what enzyme degrades either synthetic or biologic FAAH inhibitors, and this is an area where further research is warranted **(Figure 2).**



A) Selective and potent synthetic FAAH inhibitors. **B)** Chemical structures of naturally occurring FAAH inhibitors from various plant-derived sources: Biochanin A, Formononetin, Daidzein, and Genistein (flavonoids found in red clover; Trifolium pretense), Myristicin (nutmeg, anise, parsley, dill), Kaempferol (broccoli, tomatoes, grapes, green tea) Pelargonidin (all berries, plums, pomegranates), Guineensine (alkaloid found in long pepper; Piper longum), macamides N-Benzylstearamide and (N-BenzylOctadeca-9Z, 12Z-dienamide (Maca, Lepidium meyenii). Courtesy Jana Sharp.

Figure 2: Chemical structures of Synthetic and Naturally Occurring FAAH Inhibitors.

Technological limitations, coupled with a suppression of research of biologic cannabinoids at many major research universities, has resulted in a limited understanding of the endocannabinoid system. Questions still need to be answered to provide a comprehensive comparison of biologic with synthetic FAAH inhibitors. An exhaustive review of the literature provides no definitive explanation as to which natural enzyme degrades the biologic and synthetic inhibitors. Monoacylglycerol lipase (MAG) appears to be one likely culprit, but further research is needed in this area [28,29].

A determination of the enzyme is necessary to design an in vitro study to verify the theory that there is a significant difference in degradation rates between synthetic and biologic FAAH inhibitors. A difference in these degradation rates would explain the differences in adverse events exhibited in the synthetic and biologic FAAH inhibitors. Although the science concerning the efficacy of supplementing phytocannabinoids to treat deficiencies of endocannabinoids is robust and well-accepted, utilization of this knowledge is still in its beginning stages [30-32].

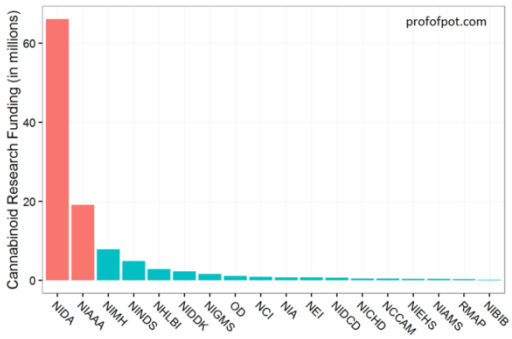
A Psychosocial Perspective of the Endocannabinoid System

Technological advancement and research aimed at understanding endogenous and exogenous cannabinoids, and particularly the medicinal properties of the Trans-Δ^9-tetrahydrocannabinol (THC) molecule, are hindered by prohibitive restrictions resulting from the mission statements of the Food and Drug Administration (FDA), Drug Enforcement Administration (DEA), National Institute of Health (NIH), and the National Institute on Drug Abuse (NIDA).

The missions of these entities effectively integrate to ensure research and utilization of the medicinal properties of THC face stiff resistance. One of the mandates of the FDA is to evaluate any medicine submitted to it provided the medicine has a synthetic (patentable) component. The mission of the NIDA is to advance science on the causes and consequences of drug use and addiction and to apply that knowledge to improve individual and public health.

NIH through NIDA has provided and continues to provide funding for studies related to therapeutic uses of cannabinoids, including THC as it pertains to its mission, but the vast majority of research proposals funded involve therapeutic benefits of individual phytocannabinoids and not the utilization of an entourage of these molecules to measurably manipulate endocannabinoid tone. NIDA predominantly funds research on the use of individual molecules due to the difficulty of standardizing dosing with full-plant preparations. As the federal agency responsible for determining which cannabinoid studies get funded and what questions remain unanswered, NIDA traditionally restricts this research to the deleterious effects of phytocannabinoid ingestion, particularly focusing on dopamine-releasing actions of the THC molecule.

NIH admits that only 19% of their research funds are slated to studying the possible therapeutic properties of phytocannabinoids, and this is with admittedly a very loose interpretation of the definition of "therapeutic" (National Institute of Health, 2018). In fiscal year 2015, NIH supported 281 projects totaling over $111 million dollars on cannabinoid research, with this funding disproportionately slated to the two Institutes with stated missions of designing studies for the purpose of exposing purported negative health effects of intromitting phytocannabinoids: The National Institute on Drug Abuse and the National Institute on Alcohol Abuse and Alcoholism [33] **(Figure 3).**



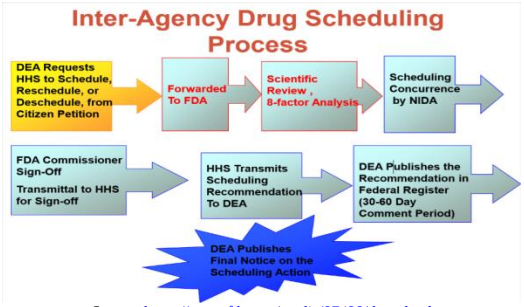
Source: https://profofpot.com/nih-funding-medical-cannabis/

Figure 3: The national institute on drug abuse and the national institute on alcohol abuse and alcoholism.

The Drug Enforcement Administration (DEA) was created in 1973 to enforce criminal penalties on individuals for using unapproved exogenous compounds to increase their dopamine levels. Unsurprisingly, the conglomeration of the missions of these four entities has the US federal government focusing much more on researching the negative effects of phytocannabinoids rather than their well-documented medicinal properties.

As of September 1, 2019, every State except Nebraska allows their residents to medicate with phytocannabinoids, with 14 of these regulating the percentage of THC. Some Idaho, South Dakota, and Indiana residents have attained access after successfully challenging their state bureaucracies.

Because of this and overwhelming public acknowledgment of the efficacy of medicinal cannabis, the general perception of the population is that federal acceptance of medicinal cannabis is imminent, but unless the application of the mission statements of the four federal agencies involved change, science must develop alternate approaches for modulating the endocannabinoid system. Even with the possible acceptance of the CBD molecule due to the erroneous claim that it lacks psychoactive properties, the utilization of the medicinal properties of THC conflict with the mission statements of each of the four bureaucratic entities that have a say in the decision concerning its legalization at the federal level [34,35] **(Figure 4).**



Source: https://www.fda.gov/media/97498/download

Figure 4: Inter agency drug scheduling process.

By mandate, unless the utilization of medicinal cannabis is legalized at the federal level, the therapeutic properties of the exogenous THC phytocannabinoid must come from increasing levels of its endogenous equivalent, anandamide. The FDA is currently working with pharmaceutical companies to establish the appropriate path forward for the synthesis of safe and effective FAAH inhibitors, but human clinical trials for these drugs are many years and many billions of dollars in the future [36]. Until the four bureaucratic agencies revise their missions to allow for the utilization of the exogenous cannabinoid the medicinal benefits inherent in THC must occur by scientists devising efficacious methods of increasing the concentration of its endogenous equivalent.

A Natural Fatty Acid Amide Hydrolase Inhibitor

Biochanin A is an isoflavone mainly found in red clover. It has poor solubility and oral absorption and exhibits various effects, including anti-inflammatory, estrogen-mimicking, and glucose lipid modulatory activity, as well as being a cancer preventive, and neuroprotectant [37-48]. It is already commercially available and among the main ingredients in many types of supplements used to alleviate postmenopausal symptoms in women.

In addition to these benefits, Biochanin A is a mixed-type inhibitor of FAAH, demonstrating low micromolar potencies towards rat, mouse, and recombinant human FAAH, sans the adverse effects so commonly associated with its synthetic counterparts. It has drawn considerable attention from researchers in recent years owing to the wide spectrum of its pharmacological activity, many related to its actions as a natural inhibitor of fatty acid amide hydrolase. FAAH is the enzyme responsible for the metabolism (degradation) of the endogenous cannabinoid receptor ligand anandamide (AEA) and many other endogenous fatty acid amides, exhibiting a distribution consistent with its role in regulating (terminating) their effects at their released sites of action.

This action provides the mechanism responsible for the effectiveness Biochanin A exhibits in treating multiple endocannabinoid deficiency disorders including Post Traumatic Stress Disorder, Autism, ADHD, Alzheimer's disease, Multiple Sclerosis, Dementia, Parkinson's disease, Huntington's disease, and scores of other nervous system disorders resulting from deficiencies in anandamide [49-52].

Thors et al. investigated a series of analogs of the isoflavones genistein and daidzein to provide illumination on the structural requirements for FAAH inhibition and to determine whether more potent natural analogs could be found. Among the analogs tested, biochanin A, was shown to be a more potent inhibitor of FAAH than genistein in vitro, and to produce biochemical effects upon a spinal cord pain signaling pathway consistent with FAAH inhibition in vivo without the adverse effects of synthetic FAAH inhibitors [53].

Issues of Bioavailability

Biochanin A has drawn the considerable attention of researchers in recent years due to its wide array of pharmacological actions including its neuroprotective, anticancer, antioxidant, anti-inflammatory, osteogenic, and anti-hyperglycemic properties. Even though the therapeutic potential of this isoflavone is intriguing and has been studied in a variety of in vitro, in vivo and ex vivo models, its potential has been deemed limited due to its low oral bioavailability. As is often the case in scientific endeavors related to biomolecular psychology, an innovative approach must be devised to adapt to identified limitations. Biochanin A is a poorly soluble bioflavonoid, and this characteristic prevents its oral absorption. While ingestion is typical for nutraceuticals, a more innovative method of intromission must be developed. Creativity is the essence of the scientific process, and new methods of intromission of medicines which increase bioavailability are constantly being devised. Transdermal patches deliver a specific dose of medication into the bloodstream through a porous membrane. An advantage of a transdermal delivery route is that a patch provides a controlled release of the compound into the subject. A wide variety of pharmaceuticals are now available in transdermal patch form, and this delivery method can easily be appropriated to enhance the bioavailability of nutraceuticals such as Biochanin A [54].

Summary

Psychosocial, political, and bureaucratic policies dictate much of the US landscape of research into endogenous and exogenous cannabinoids, particularly THC. Researchers are identifying endocannabinoid deficiency disorders and mechanisms through which treatment approaches may be developed. Endocannabinoid deficiency disorders may be effectively treated through the supplementation of equivalent phytocannabinoids. Molecular engineers are studying FAAH as a target for pharmaceuticals as controlling levels of FAAH may produce some of the same health effects that excite clinicians about the potential for phytocannabinoid-based medicines. Medicines that inhibit the body's production of FAAH are theorized to have a similar effect by maximizing the concentration of deficient endocannabinoids endogenously, but the development of potent and safe synthetic FAAH inhibitors has been hindered by their deleterious side effects. Differences in the body's ability to metabolize synthetic and biologic FAAH inhibitors are theorized to contribute to their differing safety profiles, but the biomolecular degradation mechanism remains unidentified and is an area where further research is warranted.

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