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Synthetic Cannabinoids, Organic Cannabinoids, the Endocannabinoid System, and Their Relationship to Obesity, Diabetes, and Depression

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Abstract

This disquisition is designed to be an exploration of the controversies, contentions, and consternations with regard to the efficacy and potential of a newly devised CAM approach which entails modulating the endocannabinoid system and is considered to be a potentially useful technique for the treatment of obesity and diabetes. This paper is constructed to provide the reader with an understanding of the principles underlying a form of Complimentary Alternative Medicine (CAM) which has existed for millennia but has only recently attained credibility and acceptance within the scientific community. It provides a historical analysis of the perceived equivalency between synthetic cannabinoids and organic cannabinoids as well as the unknowns of each in their potential treatment of obesity and diabetes.

Keywords: Cannabinoids; Diabetes; Obesity; Depression; Rimonabant; CAM; Receptors

Introduction

The following disquisition is designed to be an exploration of the controversies, contentions, and consternations with regard to the efficacy and potential of a newly devised CAM approach which entails modulating the endocannabinoid system and is considered to be a useful technique for the treatment of obesity and diabetes. By necessity, this exploration becomes rather convoluted because in the year 2006 traditional medicine took a shot at incorporating this CAM approach into their world-view by attempting to integrate their synthetic, single molecule paradigm into a system of incredible molecular diversity. Although the attempt failed dramatically and resulted in a large number of major depressive episodes as well as two suicides, the endeavor provided some valuable knowledge applicable to the field of bimolecular psychology.

Two ailments will be discussed, one physical and one emotional. As will be demonstrated, both are intricately interrelated, although not in a way that is immediately and intuitively apparent. The areas where our knowledge is lacking and the necessity of research in the field of biomolecular psychology will be explored which will further our understanding of the endocannabinoid system as well as how this knowledge can be incorporated into this next frontier of medicine. This paper is constructed to provide the reader with an understanding of the principles underlying a form of Complimentary Alternative Medicine (CAM) which has existed for millennia but has only recently attained credibility and acceptance within the scientific community. The approach based on the biological system was discovered less than two decades ago, and therefore the paradigm is still in its infancy. Traditionally, new paradigms in science are met with resistance even though it is a scientist's responsibility to design studies which potentially challenge the dominant world-view. However, traditionally scientists that challenge dominant paradigms are often persecuted [1]. For example, Albert Einstein struggled when attempting to gain acceptance of his theory of relativity. Galileo died under house arrest for proffering the paradigm of a heliocentric universe, and Charles Darwin is still being persecuted 160 years after he established the paradigm on which the science of biology is now based. The point is scientists at the forefront of paradigm shifts have to expect resistance from purveyors of the dominant ideology, and imaginative methods are at times utilized to combat the perceived threat of attaining new knowledge. This resistance manifested itself as a ban being imposed on the research of organic cannabinoid molecules (phytocannabinoids) in 1971, and because of this, there are gaps in our knowledge and understanding of the intersection of the endocannabinoid system with the study of psychology and medicine. Ironically, our understanding of this intersection has been greatly enhanced by the study of pharmacology and an attempt by a French pharmaceutical company called Sanofi-Aventis to treat obesity and diabetes by creating a synthetic cannabinoid designed to dominate the biological system which controls virtually every aspect of the way our minds and bodies function.

Obesity and diabetes have become health problems of epidemic proportions in the industrialized world [2,3]. More than a million and a half studies have been penned about obesity alone, and the condition is still considered extremely difficult to control in the modern world. Traditional treatments of low-calorie diets and appetite-suppressing drugs frequently fail [4]. The majority of studies reporting weight loss resulting from merely low-calorie diets report that most subjects regain the weight back either partially or completely within three to five years after treatment ends, and long-term studies present a less favorable outcome with 49.5% of subjects regaining or surpassing their previous weight [5]. These issues with traditional treatment efficacy indicate the necessity for the development of new strategies of both losing weight and maintaining that weight loss.

In a study examining the relationship between obesity and diabetes conducted by the National Health and Nutrition Examination Survey (NHANES), researchers found the prevalence of diabetes increased with escalating weight classes [6]. Other researchers also weigh in on intervention approaches for treating diabetes. "Nearly half of adult diabetics are considered obese suggesting that weight loss is an important intervention in an effort to reduce the impact of diabetes on the healthcare system." [7]. In 2012, the total healthcare cost for diagnosed cases of diabetes in the United States was 245 billion dollars. At that time it was expected the cost would soar to half a trillion dollars by the year 2020 and we as a nation are well on our way to achieving those

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projections. The total estimated cost of diagnosed diabetes in 2017 was 327 billion dollars in direct medical costs plus an additional 90 billion dollars in reduced productivity. After adjusting for inflation, economic costs of diabetes rose by 26% from 2012 to 2017 due to its increased prevalence and the increased cost per afflicted person [8]. Traditional approaches for treating diabetes involve the patient keeping close watch over their blood sugar levels and maintaining them within parameters set by their doctor, and by employing a combination of diet, synthesized medications, and exercise [9]. People with diabetes frequently use complementary and alternative medicine (CAM) techniques of multiple varieties ranging from dietary approaches to herbal and vitamin therapies, and massage. The endocannabinoid system has lately received considerable attention as a potential therapeutic target in combating obesity as well as its associated metabolic abnormalities [10]. Studies by Sanofi-Aventis Pharmaceuticals demonstrated that a simple synthetic CB1 receptor antagonist (Rimonabant) corrected the deleterious effects of diet-induced obesity by restoring insulin sensitivity and normalizing fat cell size and distribution [11]. This antagonist also prevented visceral fat accumulation and decreased subcutaneous fat. Other investigations showed similar findings and concluded that blockage of the CB1 receptors with Rimonabant decreased body weight and adiposity, independent of sustained reductions in food intake in humans, canines, and rodents [12-16].

By the year 2006 Sanofi-Aventis had conducted numerous studies which indicated the central cannabinoid (CB1) receptors played a significant role in controlling food consumption and dependence. To develop suitable synthetic medicines against this target, compounds with potential activity against this receptor were screened for inhibitory activity. Rimonabant emerged from this screening process as a potent CB1 receptor antagonist. Preclinical animal trials subsequently showed that it reduced consumption of fats and sugars which are significant contributors to weight gain. These preclinical findings were confirmed in a series of clinical studies involving over 6,000 obese subjects and carried out in both the Americas and Europe. In the United States, the FDA requires two years of safety data before approving anti-obesity medicines, and as part of their patent application process, the pharmaceutical company conducted those trials. The conclusion of the FDA meta-analysis of Rimonabant safety data indicated an increased risk for suicidal ideation in patients and two suicides were recorded across the two-year Rimonabant clinical trial program. Furthermore, an analysis of data collected from four double-blind, randomized controlled trials demonstrated that 20 mg per day of this synthetic cannabinoid increased the risk of psychiatrically adverse events, specifically, depressed mood disorders and anxiety [17-20]. These findings resulted in marketing authorization being withdrawn for Rimonabant because the adverse psychological effects could not be addressed [21]. These results beg two questions. First, what is the mechanism causing these emotional disorders? Second, would an organic phytocannabinoid CB1 receptor antagonist produce similar results? Analyzing these questions individually brings up other questions indicative of how little we know about the correlation of synthetic cannabinoid medicines with organic phytocannabinoid supplements. A comprehensive review of the literature also indicates how little we understand about Rimonabant. 2,980 studies published within the last five years classify the synthetic cannabinoid as an antagonist at the receptor, while 1,327 studies identify it as an inverse agonist. Scientific truth is not determined democratically, and the manufacturer of Rimonabant stopped answering questions about the synthetic cannabinoid in 2009 with the claim that the information is proprietary. This distinction between antagonist and inverse agonist is critical because it speaks to the mechanism causing the adverse reaction. An inverse agonist serves as a receptor blocker, precluding the attachment of anandamide, the body's natural antidepressant endocannabinoid [22]. Theoretically, blocking the attachment of anandamide to the CB1 receptor could conceivably result in depression. If merely blocking the CB1 receptor is enough to produce depression, any inverse agonist that attaches to that receptor would prohibit the attachment of anandamide. If the1327 studies are correct, and Rimonabant merely acts as a receptor blocker, its phytocannabinoid equivalent would be CBD, providing an accessible population in the United States for survey depression studies. According to data obtained by the National Conference of State Legislators (2018), only four states remain that ban access to natural CBD. Cannabinoids derived from hemp are legally marketed in the remaining states as treatment for a variety of ailments despite the long-held FDA contention that the synthetic cannabinoids are medicinal and the organic cannabinoids are among the most addictive and dangerous molecules humans can ingest. Coincidently, 20 mg is the usual suggested dose of most phytocannabinoid supplements suggested by marketers of these products in the United States, although many recommend multiple doses per day. No studies exist on whether naturally produced CBD isolates increase the risk of these adverse psychiatric reactions. There are two schools of thought on this. The first is that synthetic cannabinoids and cannabinoids produced naturally (organic cannabinoids) act on the CB1 receptors in the same way, and therefore the effects of each should be similar. The question becomes, do both the synthetic and natural CBD act on the receptors in the same way? If they do, organic CBD should also be expected to be associated with depressed mood disorders, and physicians should be alerted to these potentially severe adverse psychiatric reactions by the US Food and Drug Administration. The second school of thought advances the notion that while naturally produced CBD acts as an inverse agonist at the CB1 receptor, the enzyme Fatty Acid Amide Hydrolase (FAAH) breaks down the organic molecule faster than the synthetic, thereby reducing the depressive effects. The most useful analogy to view this way of thinking is imagining the enzyme eating something organic as opposed trying to eat something plastic.

However, no studies have been conducted comparing degradation rates of organic cannabinoids with synthetic cannabinoids and therefore, staying true to the paradigm as presented, all indications lead to the conclusion that naturally produced CBD would increase the risk of psychiatric adverse events in the same way the synthetic cannabinoid does. Differences in degradation rates between phytocannabinoids and synthetic cannabinoids is an area in which further research is necessary.

Evidence obtained from the multiple studies of Rimonabant and its depressive properties suggests that other inverse agonists at the CB1 would have depressive properties as well. However, due to the ban on research of phytocannabinoids in the United States, this has never been studied. Given the proliferation of companies marketing isolate organic phytocannabinoid supplements throughout the nation, studies looking for possible deleterious effects of these products on a population are necessary. With 92% of the nation allowing medicinal cannabinoid use, clinical and policy concerns regarding the mental health effects of organic cannabinoids should be examined regardless of the federal mandate that such studies not be allowed. Analyzing this mandate from the paradigm of synthetic cannabinoid/organic cannabinoid equivalency, it becomes apparent that a survey study of possible depressive properties of CBD isolates could easily be conducted without Federal approval. Given the fact that the population is already legally intromitting these supplements, it seems appropriate to study their effects.

The National Institute of Drug Abuse subsidizes studies designed

to prove the deleterious effects of cannabis while blocking inquiry into its potential benefits (National Institute of Drug Abuse, 2018). If Rimonabant is an antagonist at the CB1 receptor the depression mechanism is different, but a study would fit into NIDA's wheelhouse. NIDA contracts with the University of Mississippi to produce phytocannabinoids for research purposes, and from a biomolecular perspective, one of the most important studies this supply could be used for is an analysis of the mechanism by which CB1 antagonism causes depression. Theoretically, the depression could either be the byproduct of the antagonism of the CB1 directly, or the result of blocking the CB1 receptor, thereby prohibiting the binding of anandamide, the body's natural antidepressant endocannabinoid [23].

Evidence indicates that most, if not all, of the central nervous system actions of cannabinoids, whether they be plant-derived, endogenous, or synthetic are related to an affinity for binding with the CB1 receptor. If Rimonabant is an antagonist, the phytocannabinoid equivalent has been determined to be THCV [24-26]. In the phytocannabinoid world, Tetrahydrocannabivarin (THCV) appears to be an anomaly as the only known phytocannabinoid antagonist at the CB1 receptor. Of course, there are 112 other known phytocannabinoids and information is still lacking about how each acts on the body's various receptors. What we do know has to do with the "nature of science." In scientific research, it is generally the anomalies that end up being important. This has particular significance with regard to devising a CAM approach utilizing the principles of biomolecular psychology in the treatment of diabetes [27].

Manipulation of CB1 receptors with Rimonabant resulted in a significant reduction in body weight, waist circumference, triglyceride concentrations, an increase in HDL cholesterol and adiponectin concentrations and a reduced number of subjects with type 2 diabetes [28]. However, as already discussed, in 2008, marketing authorization for Rimonabant was withdrawn due to a significant increase in incidences of adverse psychiatric events [29].

Two possible phytocannabinoids equivalents to Rimonabant have been discussed, and both have significant implications concerning proper regulation of the endocannabinoid system in addition to obesity, diabetes, and depression. Cannabidiol (CBD) provides an astonishing benefit with respect to hyperglycemia, mainly through its anti-inflammatory and antioxidant properties, and modulates cardiovascular response to stress [30].

D9-Tetrahydrocannabivarin (THCV) is a naturally occurring analog of THC, but with different pharmacological effects. As with many of the phytocannabinoids it acts on the receptors differently depending on the amount intromitted. At low dose (5-7.5 mg) it antagonizes the CB1 receptors resulting in an inhibition of appetite, while at moderate to high doses (10-20mg) it acts as an inverse agonist CB2 receptor blocker and full agonist at the GPR55 receptors resulting in a regulation of blood sugar levels while reducing the body's resistance to insulin. These properties make the potential benefit of THCV and CBD, alone or in combination, very interesting molecules for study in regard to the treatment of obesity and diabetes as they have very distinct pharmacological profiles, and therefore different side effects to Rimonabant [31-33].

Recently the American Diabetes Association published a meta-analysis indicating that there may be ethnic differences of the optimal states in the relationship between insulin sensitivity and insulin response. The genetic background of Africans and East Asians makes them more and differentially susceptible to diabetes than Caucasians [34-37], and ethnic groups are more likely to use CAM as a treatment option than Caucasians [38-41]. This indicates the necessity of further study and development of CAM approaches for the treatment of diabetes which are based on sound scientific methodology, and an argument could be proffered that further studies of the endocannabinoid system could lead to methods of balancing its environment through the judicious supplementation of naturally occurring cannabinoids.

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