Chapter 1

Introduction to Recent Advances in Cannabinoid Research

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Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.85814

Abstract

On October 17, 2018, Canada became the first G20 nation to legalize the use of *Cannabis sativa* for both medicinal and recreational purposes. This change in legislation and end of prohibition are indicative of a larger global movement to understand *Cannabis*—and the bioactive chemicals present within *Cannabis* known as the cannabinoids—for its potential biomedical uses, harms, and economic values. Currently, interest in *Cannabis* and cannabinoid research is surging as the many knowledge gaps in basic biology, pharmacology, epidemiology, and clinical efficacy are identified. The purpose of this book is to summarize some leading areas of research in the cannabinoid field where knowledge gaps have been or are being actively addressed. The research described herein spans between basic biological and clinical research. As the editors of this text, we are grateful to the work of the chapter authors and their important contributions to this rapidly growing field.

Keywords: cannabinoids, *Cannabis sativa*, phytochemicals, cell signaling, animal models, clinical trials, pediatrics, epilepsy, crystallography, Tourette's syndrome

1. Introduction

Cannabis sativa has been used medicinally and recreationally for millennia by societies around the world, but our comprehension of *Cannabis* and cannabinoids from a modern perspective is still very much in its infancy [1]. The field of cannabinoid research has evolved from a curiosity following the first report of the medicinal properties of *Cannabis* in 1840 [2] to becoming a controlled product in 1925 following the signing of an international treaty controlling its trade [3] to ultimately becoming a highly active basic and clinical research discipline. The psychoactive and intoxicating constituent of *Cannabis sativa*, Δ^9-tetrahydrocannabinol (THC),

was first isolated and described by Dr. Raphael Mechoulam in 1964 [4]. Following this discovery, it was not until 1991 that a human cannabinoid receptor—later named the type 1 cannabinoid receptor (CB1R)—was identified, isolated, and cloned [5]. Other components of the endogenous cannabinoid system (ECS) were subsequently identified in rapid succession, including the endogenous cannabinoid anandamide (AEA) and 2-arachidonoylglycerol (2-AG), the type 2 cannabinoid receptor (CB2R), and the anabolic and catabolic enzymes that synthesize and degrade the endogenous cannabinoids, respectively [6]. During this period there was also a rapid growth in tool compounds (synthetic cannabinoids) to study the ECS and a race to understand the physiological and behavioral effects cannabinoids evoke *in vivo* [7]. With this rapid growth came some of the first modern preclinical and clinical data to suggest clinical efficacy of cannabinoid-based medicines in the treatment of pain, anxiety, addiction, and metabolic disorders [8], as well as preclinical and clinical data that indicated the potential harms associated with *Cannabis* use, in particular the long-term use of THC in the context of the developing brain [9]. Our understanding of *Cannabis sativa* itself was also growing during the 1990s and 2000s, with the draft sequence of the genome published in 2011 [10] and more than 220 identified constituents (>100 cannabinoids and >120 terpenes) now identified in the plant [11, 12]. Most recently, several crystal structures of CB1R were solved in 2016 and 2017 by large interdisciplinary research groups [13–15]. These crystal structures will allow for rational drug design and comprehension of drug-receptor relationships for the first time in the cannabinoid field.

Although the field of cannabinoid research has seen incredible growth during the past three decades, many questions remain unanswered. As a demonstration of the cannabinoid field's infancy, the clinically relevant pharmacological effects of morphine have been documented since 1817 [16], and the crystal structure of the μ-opioid receptor was solved in 2012 [17]. The illegal status of *Cannabis* in most constituencies has represented a significant barrier to basic, epidemiological, and clinical research. However, interest in the potential applications of cannabinoids and their biology has grown tremendously since the discovery of the ECS. What was once a field with a single manuscript in 1964 has now grown to an area averaging 1500 studies per year in a veritable gold rush into a relatively poorly characterized system. With this book, our goal is to highlight the impressive work of some researchers in this field as they address what will become the critical scientific questions of our time concerning *Cannabis*.

2. Preclinical research

This book presents a collection of chapters addressing important preclinical topics, including the utility of the zebrafish model in cannabinoid research (Chapter 1), insights derived from the structural analysis of CB1R crystal structures (Chapter 2), and the analysis of medical *Cannabis* quality traits (Chapter 3). Dr. Ellis describes the historical usage of the zebrafish model and its applicability to studies of various aspects of vertebrate and mammalian biology, including neurobiology and neurological disorders, while focusing on the role of the endocannabinoid system. Dr. Al-Zoubi et al. provide an in-depth analysis of the unique aspects of cannabinoid receptors gleaned from studies of hCB1R crystal structures. These authors

present an extensive review of studies using mutation and labeling of CB1R to characterize the orthostatic binding site and identify issues with crystal structures that could impact their utility in rational drug design. Dr. Calvi et al. provide a description of state-of-the-art analytical methods used to assess the quality attributes of medical *Cannabis* products. This is a particularly timely topic as the necessity to characterize *Cannabis* chemotypes has increased with the recent legalization and regulation of medicinal *Cannabis* in major markets around the world.

3. Clinical research

The clinical research described in this book focuses on the clinical effects of *Cannabis* and cannabinoids on cognition (Chapter 4), the treatment of pain (Chapter 5), Tourette's syndrome (Chapter 6), *Cannabis* use disorder and *Cannabis* withdrawal (Chapters 7 and 8), cannabinoid dosing considerations in pediatric populations (Chapter 9), and *Cannabis* use for treating pediatric and adult epilepsy (Chapter 10). Dr. Weston-Green provides a comprehensive overview of cannabinoid-dependent effects on cognition, including discussions about (1) the many "lesser-known" plant cannabinoids beyond THC and cannabidiol that have been under-assessed to date and (2) the potential "entourage effects" of cannabinoid combinations occurring in *Cannabis* products. Dr. Uhelski et al. review the anti-nociceptive properties of cannabinoids and the preclinical as well as clinical evidence for the use of cannabinoids as analgesics for peripheral pain. *Cannabis*-based medicines (CBM) are presently being examined for a wide array of psychiatric conditions for which the evidence base is small yet growing. Dr. Szejko provides a review of the clinical evidence for CBM in Tourette's syndrome and the potential mechanisms of action at work for cannabinoids in this disorder. *Cannabis* and the ECS are now recognized for their potential to treat substance abuse disorders, including opioid addiction and *Cannabis* use disorder itself. Dr. Balodis et al. provide a comprehensive review of *Cannabis* use disorder, its epidemiology, potential harms, and other important considerations. Dr. Ferreira et al. review the potential of cannabinoids—including novel bioligands—to treat substance use disorders. At long last, cannabidiol is now recognized and accepted as an anticonvulsant medication for the treatment of refractory pediatric epilepsies, such as Dravet and Lennox-Gastaut syndromes, with the recent FDA approval of Epidiolex® for these conditions. In the final chapters of this book, Dr. Huntsman et al. review the clinical evidence for high-cannabidiol *Cannabis* herbal extracts for the treatment of pediatric and adult epilepsies, while Dr. Alcorn et al. review critical dosing considerations and pharmacokinetic parameters for *Cannabis* in the pediatric population.

4. Looking forward

Basic and clinical cannabinoid research has recently become a greater priority due to the increasing number of jurisdictions where legalization of *Cannabis* use for both medical and recreational purposes has occurred. There have been numerous health claims attributed to *Cannabis*, and the evidence supporting some of the claims remains inconclusive. According

to the conclusion of a report by a Committee On The Health Effects Of Marijuana, the therapeutic benefit of *Cannabis* on chronic pain, chemotherapy-induced nausea and vomiting, and multiple sclerosis spasticity has been deemed effective, whereas insufficient evidence was available to support a similar conclusion in the treatment of cancer, anorexia and weight loss, irritable bowel syndrome, epilepsy, spinal cord injury-induced spasticity, Tourette's syndrome, amyotrophic lateral sclerosis, Huntington's disease, Parkinson's disease, dystonia, dementia, glaucoma, traumatic brain injury or intracranial hemorrhage, addiction, anxiety, depression, sleep disorders, posttraumatic stress disorder, schizophrenia, and other psychoses [8]. Thus, while tremendous advances have been made in understanding the biology of the ECS and of *Cannabis sativa*, it is clear that many aspects of the medical use of *Cannabis* require further clarification. Additionally, there has been a marked increase in the generation of novel synthetic cannabinoids over the last decade [18], the general availability of which has prompted concern among regulatory agencies due to their unknown safety profiles [19, 20]. This is highlighted by the rapidly increasing number of case reports detailing the effects of acute synthetic cannabinoid intoxication [21–23]. The potential dangers of synthetic cannabinoid use are attributable to the intrinsic properties of these substances and their metabolites. The potential for harm is further exacerbated by the poor pharmacological and toxicological characterization of synthetic cannabinoids. Thus, intensified research efforts into the health benefits and harms of *Cannabis* and cannabinoids will hasten the positive exploitation of *Cannabis* and reduce the drawbacks of *Cannabis* and synthetic cannabinoids.

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