Therapeutic Use of Synthetic Cannabinoids: Still an Open Issue?

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ABSTRACT

Cannabis sativa has a long history of use for medical purposes despite marijuana's addictive potential. The discovery of the endogenous cannabinoid system as a neuromodulatory system composed of receptors, endogenous ligands (endocannabinoids), and enzymes responsible for their synthesis and degradation, together with recent advancements in the elucidation of cannabinoid pharmacology, has renewed interest in medicines acting on the endocannabinoid system. Synthetic cannabinoid agonists have been developed and used for treatment of different human pathologic conditions, and promising potent cannabinoid antagonists are currently under clinical evaluation. During the last decade, new generations of synthetic cannabinoids appeared on the global drug market, proposed as marijuana-like compounds and sold as herbal mixture also known as spice drugs or legal highs. Because activation of cannabinoid receptors may induce central and peripheral beneficial effects, the newest synthetic cannabinoids having full agonistic activity and high potency at cannabinoid type 1 and type 2 receptors might have therapeutic potential too. However, case reports of acute and fatal intoxications are accumulating and revealing that this is not the case because adverse effects of the latest generation of synthetic cannabinoids far exceed the desired ones. (*Clin Ther.* 2018;■:1–10)

Key words: medical cannabis, spice drugs, synthetic cannabinoid, therapeutic potential.

INTRODUCTION

The progress of innovative life-saving and life-improving medications is one of the major goals of pharmaceutical investigations at any level of research, from academia to industry. Drugs originally discovered in biotechnology companies or universities accounted for approximately half of the scientifically innovative drugs approved by the US Food and Drug Administration (FDA) from 1998 to date. Early-stage discoveries, preclinical findings, and translational medicine, which improve the transition from basic research to applied clinical research and commercialization, are steps necessary for most classes of drugs and cover more than a decade with a mean cost of US$2.6 billion.[1–3]

In 1964, Raphael Mechoulam at the Hebrew University of Jerusalem isolated Δ9-tetrahydrocannabinol (THC) from hashish.[4] Together with his collaborators, he then described the chemical structure and partial synthesis of THC and explained the structure-activity relationship in the THC series.[5] From that time, >50 years of prosperous cannabinoid research developed on 3 main aspects: (1) the discovery of cannabinoid receptors and synthesis of selective agonists and antagonists, (2) the individuation of endogenous ligands (ie, endocannabinoids) and of their biosynthesis and degradation pathways, and (3) the possibility to manipulate the endogenous on-demand cannabinoid signaling for therapeutic purposes. The experimental approach to study the cannabinoid type 1 (CB_1) receptor and the psychoactive effects of THC consisted of in vitro and in vivo animal studies, including binding studies and functional assays[6,7] and behavioral tests (eg, ataxia in dogs, tetrad test in mice).[8]

The synthesis of selective cannabinoid receptor agonists with particular reference to their antinociceptive activity started at Pfizer in 1974 with cyclohexylphenol CP 55940 followed by the HU-210 compound

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synthetized in 1988 by Mechoulam's group at the Hebrew University and supposed to be a nonpsychotropic cannabinoid[9] (Table I). Naphtoylindoles such as WIN 55212-2 synthesized at Sterling-Winthrop and JWH-018 synthetized by John W. Huffman at the Clemson University in South Carolina followed soon after (in 1994). In addition, cannabinoid receptor antagonists were developed with therapeutic purposes, among which the most studied and used clinically is probably rimonabant (SR141716A), which was discovered and developed by Sanofi-Aventis and approved in Europe in 2006 to treat obesity. Indeed, rimonabant induces weight loss, increases HDLs, and reduces triglycerides, abdominal fat, fasting glucose, and fasting insulin in patients with metabolic syndrome.[10] In addition, clinical trials were performed to assess its properties on cannabis withdrawal and dependence (Phase I), alcoholism (Phase II), and atherosclerosis and Prader-Willi syndrome (Phase III) (www.clinicaltrials.gov). Nevertheless, in Europe, rimonabant was withdrawn from the European Medicines Agency in 2008 because of increased incidence of depression, anxiety, and suicidal ideation. However, other promising potent cannabinoid antagonists were developed for the treatment of obesity and then tested in clinical trials for different purposes (Table I). CP-945598 (otenabant), for example, was developed by Pfizer originally to treat obese patients, but then it was considered beneficial for patients with nonalcoholic steatohepatitis. Another cannabinoid antagonist, SR147778 (surinabant), developed by Sanofi-Aventis, was found to be useful in the treatment of nicotine dependence, whereas AVE1625 (drinabant, Sanofi-Aventis) is undergoing clinical development for the treatment of cognitive impairment in patients diagnosed with schizophrenia and mild Alzheimer disease. Notably, between 2010 and 2014, a total of 32 controlled studies were performed to investigate the potential therapeutic properties of smoked cannabis, oral THC, sublingual nabiximol, and oral cannabidiol.[11]

In addition to activation or blockade of CB_1 receptors, another intriguing therapeutic approach is represented by the use of metabolic enzymes, such as inhibitors of the fatty acid amide hydrolase (FAAH) or monoacylglycerol lipase (MAGL), that prevent degradation of the 2 endocannabinoids anandamide [(5Z,8Z,11Z,14Z)-*N*-(2-hydroxyethyl)-5,8,11,14-icosatetraenamide] and 2-arachidonoylglycerol (2-AG) [1,3-dihydroxy-2-propanyl (5Z, 8Z,11Z,14Z)-5,8,11,14-icosatetraenoate], respectively. Other compounds that alter endocannabinoid metabolism, such as URB597, also known as KDS-4103, URB694, PF-04457845, ARN14633, and JZL184, have also been studied. Contrary to the encouraging preclinical data, recent clinical defeats of endocannabinoid-related therapies have been reported.[12] Impressively, in January 2016, the FAAH inhibitor BIA 10-2474 developed by Bial (Portela & C.ª, S.A., São Mamede do Coronado, Portugal) produced serious adverse events in 6 participants of a Phase I clinical trial; the highest dose tested (50 mg) produced the most serious symptoms associated with a single case of coma, which rapidly led to brain death, whereas 2 of the other 5 participants had serious neurologic damage.[13] In fact, FAAH and MAGL are not selective enzymes and degrade a wide range of lipid signaling molecules not necessarily related to the endocannabinoid system. Moreover, endocannabinoids are metabolized by many other enzymes, including cyclooxygenases. Thus, although increasing the levels of endocannabinoids rather than activating cannabinoid receptors exogenously is likely to reduce adverse events, the full suppression of endocannabinoid catabolic enzyme activity is not an effective therapeutic approach because of the implicit cascade of adverse effects. However, preclinical research is still ongoing, providing discrepant results. For example, the new FAAH inhibitor, AM3506, was recently reported to produce THC-like impairments in a rat model of working memory, whereas other FAAH inhibitors, such as URB597, URB694, PF-04457845, ARN14633, and JZL184, had no effect on accuracy.[14] On the other hand, another study found that the new dual MAGL/FAAH inhibitor, AM4302, is an effective treatment for acute and anticipatory nausea in rats.[15] Moreover, MAGL inhibition by JZL184 did not affect food taking or nicotine reinforcing properties in rats,[16] whereas dual FAAH-MAGL inhibition by SA-57 was recently found to induce antinociceptive effects and reduce heroin reinforcing properties.[17]

PHARMACEUTICAL DEVELOPMENTS OF SYNTHETIC CANNABINOIDS

The discovery of the psychoactive properties of the natural or synthetic CB_1 receptor agonists stimulated interest in the development of new therapeutic agents that act as agonists at the CB_2 receptors and avoid of psychoactive effects. However, efforts of >20 years of medicinal chemistry studies were not sufficient to discover or synthetize a compound able to dissect CB_1-