Review

Cannabis: From a Plant That Modulates Feeding Behaviors toward Developing Selective Inhibitors of the Peripheral Endocannabinoid System for the Treatment of Obesity and Metabolic Syndrome

Shira Hirsch and Joseph Tam *

Obesity and Metabolism Laboratory, Institute for Drug Research, School of Pharmacy, Faculty of Medicine, The Hebrew University of Jerusalem, Jerusalem 9112001, Israel; shirah@ekmd.huji.ac.il
* Correspondence: yossit@ekmd.huji.ac.il; Tel.: +972-2-675-7645

Received: 24 April 2019; Accepted: 12 May 2019; Published: 15 May 2019

Abstract: In this review, we discuss the role of the endocannabinoid (eCB) system in regulating energy and metabolic homeostasis. Endocannabinoids, via activating the cannabinoid type-1 receptor (CB1R), are commonly known as mediators of the thrifty phenotype hypothesis due to their activity in the central nervous system, which in turn regulates food intake and underlies the development of metabolic syndrome. Indeed, these findings led to the clinical testing of globally acting CB1R blockers for obesity and various metabolic complications. However, their therapeutic potential was halted due to centrally mediated adverse effects. Recent observations that highlighted the key role of the peripheral eCB system in metabolic regulation led to the preclinical development of various novel compounds that block CB1R only in peripheral organs with very limited brain penetration and without causing behavioral side effects. These unique molecules, which effectively ameliorate obesity, type II diabetes, fatty liver, insulin resistance, and chronic kidney disease in several animal models, are likely to be further developed in the clinic and may revive the therapeutic potential of blocking CB1R once again.

Keywords: Cannabis; marijuana; CB1 receptor; central CB1 receptor blockade; peripheral CB1 receptor blockade

Key Contribution: This paper provides an overview of the regulatory role that cannabinoid-1 receptor (CB1R) plays in feeding behaviors in the central nervous system and metabolism and energy homeostasis in peripheral organs. Emphasis is placed on the preclinical development of novel drugs that block CB1R in the periphery to ameliorate obesity, type II diabetes, fatty liver, and chronic kidney disease by counteracting the enhanced ‘endocannabinoid tone’ found in these metabolic abnormalities.

1. Overview of Plant Cannabinoids and Endocannabinoids

Throughout human history, plants have been used as a predominant source of medications. The genus Cannabis includes up to three strains, Cannabis sativa, Cannabis indica, and Cannabis ruderalis, each with a very long history of domestication [1]. These strains can be separated by morphology, by phytochemistry, and by differences in their original geographic area. Hybrid variations of these strains have been developed to strengthen some specific characteristics in order to make cannabis an effective drug [2]. Regarding its unique chemistry, Cannabis sativa (marijuana) is considered one of the most resourceful plants, research investigations of which during the past half-century have led to the discovery of an important homeostatic system, the endocannabinoid (eCB) system, which plays a key role in human physiology (reviewed in [3]). Currently, 545 natural compounds have
been identified from this plant [4]. Of these, 144 have been isolated and identified as cannabinoids (phytocannabinoids) [5]. The first attempt to successfully identify a cannabinoid was made in 1899 by Wood and colleagues [6], who isolated cannabinol (CBN). However, it took almost forty years and several groups’ efforts to identify the correct structure of CBN (reviewed in [7]). Interestingly, the most advanced characterization of different phytocannabinoids was done during the 1960s by Mechoulam’s group, who isolated and reported the correct structure and stereochemistry of cannabidiol (CBD) [8], Δ9-tetrahydrocannabinol (Δ9-THC, the main psychoactive component of marijuana) [9,10], Δ8-tetrahydrocannabinol (Δ8-THC) [11], cannabigerol (CBG) [12], cannabichromene (CBC) [13], and cannabicyclol (CBL) [14].

Since then, three decades had passed until the binding sites of Δ9-THC in the brain and peripheral organs were identified, which were then termed as the cannabinoid-1 and -2 receptors (CB1R and CB2R, respectively) [15–17]. As of recently, their structures have been cloned and reported by several groups [18–21]. These characterizations will significantly aid in developing more specific synthetic cannabinoids in the future. Signaling by both receptors is mainly mediated via Gαi/Gαs proteins, despite the fact that they can also recruit Gβγ and Gq11 proteins and facilitate G protein-independent molecular pathways [22]. CB1R, primarily localized in the cell membrane, is the most widely expressed G-protein coupled receptor (GPCR) in the human brain [23], but it is also abundantly expressed in peripheral organs [24]. CB2R, on the other hand, is predominantly localized in immune cells and is moderately expressed in many peripheral tissues, with conflicting evidence regarding its expression in the central nervous system (CNS) [25]. Of the 144 phytocannabinoids present in Cannabis, only Δ9-THC and its less abundant propyl analogue, Δ8-tetrahydrocannabivarin (THCV), have been shown to bind to CB1R and CB2R with high affinity (with agonistic and antagonistic activity for THC and THCV, respectively). Regarding other cannabinoids, studies have shown their ability to bind to several different receptors, ranging from other GPCRs (GPR18, GPR55, and GPR119) to ion channel (thermosensitive transient receptor potential (TRP) channels) and nuclear receptors (peroxisome proliferator-activated receptors, PPARs) (reviewed in [26]); however, their physiological functions are still largely unknown.

The successful cloning and identification of CB1R and CB2R in mammalian cells prompted the discovery of their first endogenous ligand, arachidonyl ethanolamide (AEA, or anandamide) [27], which was then followed by identifying 2-arachidonoyl glycerol (2-AG) [28,29]. Whereas AEA is a high-affinity, partial agonist of CB1R and barely active at CB2R, 2-AG is known to activate both receptors with moderate-to-low affinity [30,31]. Both eCBs are synthesized, transported, and inactivated in their respective target tissues differently. Whereas AEA is catalyzed from N-acyl-phosphatidylethanolamine (NAPE) by NAPE-specific phospholipase D (NAPE-PLD) or via other means [3], 2-AG is mainly generated from diacylglycerol (DAG) by either DAG lipase (DAGL) α or β [32]. Their degradation depends on the specific cellular uptake and enzymatic catabolism. AEA is degraded primarily by membrane-associated fatty-acid amide hydrolase (FAAH) into free arachidonic acid and ethanolamine [33], whereas 2-AG is predominantly hydrolyzed by monoglyceride lipase (MAGL) into arachidonic acid and glycerol [34].

The eCB system, acting both centrally and peripherally, is an important physiological system, comprising the cannabinoid receptors and their natural endogenous ligands as well as the enzymes/proteins involved in their biosynthesis, transport, and degradation. It is involved in many physiological and pathological conditions and functions as a regulatory homeostatic system in various tissues, such as the brain, skin, liver, cardiovascular system, bone, kidney, pancreas, adipose and muscle tissues, the digestive track, and many more (reviewed in [3]). Since it is ubiquitously present in humans and animals, it has been suggested that its homeostatic roles are “relax, eat, drink, rest, sleep, save, store, forget, and protect” [35]. Therefore, changes in eCB ‘tone’, represented by the expression of the cannabinoid receptors, their functional activity (upregulated or downregulated), and the relative amount of eCBs, may render the subject susceptible to different diseases. For instance, enhanced eCB ‘tone’ has been linked to the development of many metabolic diseases (e.g., obesity, type II diabetes, fatty liver disease, and chronic kidney diseases) [24], whereas reduced eCB ‘tone’, also
termed ‘clinical eCB deficiency syndrome’, is associated with migraine, fibromyalgia, irritable bowel syndrome, schizophrenia, multiple sclerosis, Huntington’s, Parkinson’s, anorexia, chronic motion sickness, and autism [36–38]. Therefore, utilizing different approaches to achieve modulatory effects on the eCB system and ‘normalize’ its action under these conditions (by using various phytocannabinoids, synthetic cannabinoids, and novel drugs that may affect eCB ligand synthesis or degradation) is advised.

2. Is Marijuana a Toxic Drug?

Cultivated for millennia, marijuana still has a remarkable ability to alleviate different physical pathologies. To date, the U.S. Federal Food, Drug, and Cosmetic Act defines marijuana as a drug, taken by either smoking or consuming it orally for therapeutic purposes. As a drug, it may also cause harm and has toxic effects. Thus far, only limited reports related to the side effects of marijuana used for medical purposes have been reported. This contradicts the existing information regarding its recreational use, as well as in comparison to other drugs (e.g., morphine and cocaine). Whereas the latter drugs may cause death when consumed inappropriately, mainly due to respiratory arrest [39,40] and/or increasing the blood pressure and heart rate [41,42], no such evidence has been reported with the use of marijuana. Nevertheless, a few generalized findings are related to the acute and chronic side effects of cannabis use. Among them, cannabinoids have been shown to affect: (i) the cardiovascular system (acute use is associated with tachycardia and increased blood pressure vs. chronic exposure that results in the opposite effects); (ii) the respiratory system, in which inflammation of the lungs and large airways is increased; bronchitis and emphysema have been documented with the chronic use of cannabis; (iii) cognition, by reducing attention, sensory perception, task acquisition, and working memory; and (iv) mental illness and psychiatric conditions, including depression, anxiety, psychosis, bipolar disorder, and schizophrenia (summarized in [43–46]).

3. “To Eat or Not to Eat”: The Role of Cannabinoids in Feeding Behaviors

Although not toxic, a common ‘side effect’ of cannabis use is an increase in appetite. This well-known property, coupled with the existence of CB1R within appetite-related brain areas [47], suggests that the eCB system plays a key role in regulating feeding and body weight. For centuries, marijuana has been recognized as a food intake stimulant. Although the first evidence of cannabis use for treating appetite loss was reported in 300 A.D. in India, a few studies conducted in humans during the 20th century firmly supported the ability of cannabis consumption to induce hyperphagia and snacking (collectively referred to as ‘the munchies’; summarized in [48]). Indeed, marijuana use in healthy normal volunteers has been shown to increase daily caloric intake, which is mainly because of enhanced food intake between meals rather than an increase in meal size [49]. Orally administered Δ9-THC or cannabis smoking enhances the consumption of highly palatable and sweet snack foods and increases the qualitative ratings of hunger [49–51], findings that support the role of the eCB/CB1R system in regulating feeding behaviors via the reward system [52]. These cumulative data actually support the clinical evaluation and testing of cannabinoid therapeutics to stimulate appetite in cancer patients undergoing chemotherapy [53], individuals with HIV/AIDS [54–57], and anorexia nervosa [58] as well as in anorexic Alzheimer’s disease patients [59,60].

Accumulating basic evidence also supports the orexogenic effects of cannabinoids, demonstrating increased food intake by administering Δ9-THC in various animal models [61–65]. However, our current understanding of cannabinoid action on food intake was revolutionized after CB1R was identified in various brain regions, including the hypothalamus, which plays a key role in homeostatic regulation. Indeed, direct activation of CB1R by AEA has been shown to stimulate food intake [66–69]. Other CB1R agonists were also reported to increase sucrose consumption [64,70] and hyperphagia [71]. An interesting observation reporting hypophagia induced by high doses of Δ9-THC was reported in 1975 [72]. In fact, Chopra and Chopra reported in 1939 that while a weak cannabis preparation stimulates appetite, more potent cannabis preparations usually have an opposite effect [73]. Similarly, Bouquet also noted that progressive anorexia develops with chronic use of cannabis [74]. Further
studies conducted in animals confirmed that cannabinoid administration in high doses induces hypophagia (summarized in [75]). Data on cannabis use, caloric intake, and body mass index (BMI) establish conclusive evidence that chronic cannabis use is associated with reduced BMI and obesity rates (summarized in [76]). Interestingly, despite having a lower BMI, most cannabis users appear to have increased caloric intake. This paradox can be causatively explained by the fact that heavy cannabis use results in downregulation of CB$_1$R [77–79], which in turn may lead to weight loss [76].

In keeping with this explanation, in recent years, many studies have examined how antagonizing CB$_1$R affects feeding behavior and subsequently induces weight loss in obese individuals.

4. Targeting CB$_1$R for Treatment of Obesity: Block Centrally or Inhibit Peripherally

Empirical studies in various animal models indicate that pharmacological blockade of CB$_1$R with the first-in-class synthetic CB$_1$R inverse agonist rimonabant (SR141716A) does indeed reduce weight gain and food intake in a dose-dependent manner under both fasted and non-fasted conditions [61,80–83] as well as inhibit the motivation for palatable food [84,85]. These data, together with the fact that animals genetically lacking CB$_1$R are hypophagic and lean [86], led to the idea that CB$_1$R blockade could be considered as a therapeutic tool against obesity and metabolic syndrome. Indeed, rimonabant was proven effective not only in decreasing food intake and body weight, but also in ameliorating obesity-induced insulin and leptin resistance, improving glucose homeostasis and dyslipidemias, as well as decreasing hepatic steatosis in obese/overweight individuals with metabolic syndrome [87–93]. These clinical studies led to the approval of rimonabant by the European Medicines Agency (EMA) in 2006 as an antiobesity drug under the name of Acomplia® (Sanofi-Aventis). However, growing evidence of anxiety, depression, and suicidal ideation, which was reported in a small but significant portion of individuals treated with rimonabant [94], led to its eventual withdrawal from the market in 2009. This decision affected all the big pharmaceutical companies that were developing their own CB$_1$R blockers, and questions were raised regarding the therapeutic relevance of this class of molecules in modulating the eCB system for treatment of metabolic syndrome [95].

Despite having only a transient inhibitory effect on feeding, rimonabant was very efficacious in reducing body weight and adiposity, suggesting that CB$_1$R blockade not only affects CNS-mediated energy homeostasis, but also regulates energy balance via peripheral mechanisms [96]. As mentioned before, CB$_1$Rs are present not only in the CNS, but also in many peripheral organs. Their expression levels in adipose tissue, liver, skeletal muscle, kidney, and pancreas are elevated under obese/diabetic conditions [97–103]. A parallel elevation in tissue and circulating eCB levels in obesity has also been vastly documented [100,102,104–111]. By utilizing several genetic models with a specific deletion of CB$_1$R in liver, adipose tissue, kidney, pancreas, and skeletal muscle, studies have shown that CB$_1$R modulates peripheral metabolic function. Interestingly, deletion of hepatic CB$_1$R was sufficient to protect obese mice from hepatic steatosis and dyslipidemia, as well as insulin and leptin resistance [100]. A specific deletion of CB$_1$R in adipocytes resulted in complete protection from diet-induced obesity in mice [112]. Beta cell-specific CB$_1$R-knockout mice are protected from high-fat/high-sugar diet-induced pancreatic dysfunction and inflammation [113], and its specific ablation from skeletal muscle protects mice from diet- and age-induced insulin resistance [114]. Recently, we have shown that diabesity-induced renal abnormalities are mediated via CB$_1$R specifically located on the renal proximal tubule cells (RPTCs) [102,115,116]. Whereas obese or diabetic mice lacking CB$_1$R in the RPTCs gain weight and show metabolic impairment similar to their wild-type control animals, they remain completely protected from diabesity-induced renal dysfunction, inflammation, fibrosis, lipotoxicity, and mitochondrial function [102,115,116]. Taken together, the apparent increase in peripheral eCB ‘tone’ in obesity and the key role CB$_1$R plays in cellular/metabolic regulation in many peripheral organs suggest that targeting CB$_1$R in peripheral organs by limiting brain access of CB$_1$R blockers may improve their therapeutic efficacy via reducing their potential to cause CNS-mediated adverse effects. This idea was tested experimentally in numerous studies describing the contribution of
the peripheral eCB/CB₁R system to the development of obesity and its metabolic comorbidities, as well as the therapeutic potential of peripherally restricted CB₁R antagonists to treat obesity and its sequelae.

5. Current View Regarding Novel Peripherally Restricted CB₁R Blockers

Identifying novel and robust peripherally restricted CB₁R antagonists devoid of brain penetration and CNS activity can be achieved by using two main paradigms: First, chemical modification of brain-penetrating CB₁R blockers, such as rimonabant or other rimonabant-like compounds (such as tamarabant, otenabant, ibipinabant, etc.); second, usage of computational or in vitro chemical tools to design and synthesize compounds that do not penetrate the blood–brain barrier (BBB), based on studies that characterize those properties responsible for brain penetration [117]. In both models, one should take into consideration the physicochemical properties (e.g., lipophilicity, hydrogen bonding capacity, molecular weight, and polar surface area) required for brain restriction, as well as the usage of efflux transporters, which may also depend on the compound’s structure. The preferred conditions for peripherally restricting CB₁R blockers are well-described elsewhere [118]. In brief, such a compound needs to be less hydrophobic and more polar in nature to make it impenetrable into the CNS, two properties that mainly govern passive diffusion of a molecule through the BBB [119,120]. To date, various novel molecules with peripheral selectivity toward CB₁R and limited BBB penetration have been designed and patented by different groups (summarized in [121]; Table 1). Only those that have been characterized and tested experimentally against obesity are highlighted in the following paragraphs.

AM6545 was the first to undergo a detailed pharmacological, metabolic, and behavioral assessment in murine models of obesity. This molecule ameliorates hepatic steatosis, increases insulin sensitivity, and improves dyslipidemia in diet- and genetically induced obese mice [122]. In addition, AM6545 has been shown to reduce food intake, the meal size, the rate of feeding, and body weight in obese animals [123–125]; attenuate obesity-induced dyslipidemia via activating brown adipose tissue [126]; and reverse monosodium glutamate-induced hypometabolic and hypothalamic obesity in mice [127]. Soon after, another well-characterized novel peripherally restricted CB₁R antagonist, JD5037, was developed and preclinically tested against obesity. JD5037 was found to be equally efficacious in reducing body weight and food intake, improving glycemic control, and attenuating hepatic steatosis with its brain-penetrating parent compound SLV319 (Ibipinabant®) [128]. Its hypophagic role is most likely mediated via increasing hypothalamic leptin sensitivity, although it is inactive on brain CB₁Rs [128,129]. More recently, JD5037 was found to reduce hyperphagia and weight gain in Magel2 null mice, a well-established model of Prader–Willi syndrome [109], as well as to reverse fatty acid flux-, CB₁R-, and type I diabetes-induced renal impairment [102,116].

A few other novel molecules that mostly target CB₁R in the periphery have also been synthesized and characterized, although not to the same extent as AM6545 and JD5037. Among these, TM38837, also recently termed BPR0912, has a negligible impact on brain CB₁R when tested in mice, primates, and healthy individuals [130–132], and has been shown to decrease body weight in rodents [133,134] and improve the cardiometabolic complications associated with obesity via increasing thermogenesis in white and brown adipose tissues [135]. NESS06SM, a peripherally selective CB₁R neutral antagonist whose structure is related to rimonabant, was found to be efficacious in ameliorating diet- and olanzapine-induced obesity and its metabolic abnormalities [136,137]. LH-21, initially considered as a neutral peripherally restricted CB₁R blocker able to reduce food intake and body weight in rats [138–140], was recently found to penetrate the BBB and reduce food intake in CB₁R null mice [141]. URB447 lowers food intake and body weight in mice [142], probably via reducing fat ingestion through the gut [143,144] in a CB₁R-dependent manner. With an IC₅₀ value of 159 nM, Compound 1, described by Son and colleagues in 2010, was found to be less brain-penetrating and efficacious than rimonabant in ameliorating food intake and obesity in mice [145]. With a considerably lower exposure in the brain, Compound D4, developed by 7TM Pharma, induced pronounced weight reduction in a dose-dependent manner in obese mice in comparison with rimonabant [146]. Although designed to be a P-glycoprotein (P-gp) substrate in order to decrease its brain penetration, Compound 6a, developed
by Janssen Research & Development, accumulated in the brain following chronic administration, suggesting that its in vivo metabolic efficacy cannot exclude blocking central CB₁Rs [147]. Compound 2p, which originated from the brain-penetrant CB₁R inverse agonist program of the same group, reduced glucose levels without centrally mediated behavioral effects and a reduction in food intake or body weight [148]. Lastly, TXX-522, a newly synthesized compound that exhibited minimal brain penetration while retaining high affinity and selectivity toward CB₁R, improved dyslipidemia, glucose homeostasis, and fat mass in obese mice without affecting their food intake [149]. Overall, CB₁Rs located in the periphery can be potentially considered as clinically relevant targets for therapeutics against obesity and its comorbidities, thus warranting further preclinical development and clinical testing of the peripherally restricted CB₁R blockers. Of note, in December 2017, the U.S. Food and Drug Administration (FDA) cleared the Investigational New Drug (IND) Application for JD5037 to begin Phase 1 clinical trials. However, it remains to be seen if this novel compound will clear the way for other molecules that target peripheral CB₁Rs to be fully translated into use for humans and rekindle the spark for discovering new blockbuster therapies against metabolic syndrome.
Table 1. List of peripherally restricted cannabinoid type-1 receptor (CB1R) antagonists.

| Compound   | IC_{50} = 76.9 nM | IC_{50} = 6.56 µM | Neutral antagonist | LogP/LogP | TPSA/PSA (Å²) | HBD | Animal Model | Efficacy | Brain/Plasma Ratio | Structure | Ref. |
|------------|-------------------|-------------------|-------------------|-------------|--------------|-----|--------------|---------|-------------------|-----------|-----|
| LH-21      | EC_{50} = 313 nM  | IC_{50} = 41 nM   | Neutral antagonist (CB1R)/agonist (CB2R) | LogP = 6.39 | PSA = 48.02  | N/A | ob/ob mice  | Reduces food intake and body weight gain | N/A      | [142–144] |
| URB447     | IC_{50} = 313 nM  | IC_{50} = 41 nM   | Neutral antagonist (CB1R)/agonist (CB2R) | LogP = 6.39 | PSA = 48.02  | N/A | ob/ob mice  | Reduces food intake and body weight gain | N/A      | [142–144] |
| AM6545     | IC_{50} = 3.3 nM  | CB1R/CB2R > 100   | Neutral antagonist | LogP = 3.3  | PSA = 116   | 1   | DIO C57BL/6 mice | Reduces body weight, hepatic triglyceride content, and hepatocellular damage; increases fat oxidation | 0.03     | [122–127] |
| Compound   | IC_{50} = 159 nM  | >10 µM            | Antagonist        | N/A         | N/A         | N/A | DIO C57BL/6 mice | Reduces body weight and suppresses DIO-induced elevation in hepatic SREBP-1 expression | CLapp., uptake = 0.00228 | [145] |
| Compound   | IC_{50} = 2.6 nM  | CB1R/CB2R > 1000 nM | Antagonist        | N/A         | N/A         | N/A | DIO C57BL/6 mice | Reduces body weight | 0.098    | [146] |
| TM38837    | IC_{50} = 8.5 nM  | EC_{50} = 18.5 nM | Antagonist        | LogP = 8.91 | TPSA = 78   | 1   | DIO C57BL/6 mice | Decreases body weight and increases thermogenesis | 0.03     | [130–135] |
| Compound     | CB1R Ki/EC50/IC50 | CB2R Ki/EC50/IC50 | Nature of Compound | cLogP/LogP | TPSA/PSA (Å²) | HBD | Animal Model | Efficacy                                                                                                                                  | Brain/Plasma Ratio | Structure | Ref.          |
|--------------|------------------|------------------|-------------------|------------|---------------|-----|--------------|------------------------------------------------------------------------------------------------------------------------------------------|-------------------|-----------|---------------|
| JD5037       | Ki = 0.35 nM     | CB2R/CB2R > 700 nM | Inverse agonist   | cLogP = 6  | PSA = 117     | 3   | DIO C57BL/6 mice | Reduces food intake, body weight, and improves hormonal/metabolic abnormalities                                                        | 0.02              | ![Structure](image1) | [102,109,116,128,129] |
| Compound 14h | Ki = 5.1 nM       | Ki > 10,000 nM   | Antagonist        | LogP = 3.7 | N/A           | N/A | DIO Sprague-Dawley rats | No metabolic effect                                                                                                                      | 0.13              | ![Structure](image2) | [150]         |
| NESS065M     | Ki = 10.25 nM     | Ki > 5000 nM     | Neutral antagonist | cLogP = 4.62 | TPSA = 59.39  | N/A | DIO C57BL/6 mice | Reduces body weight and visceral fat mass, improves blood glucose and dyslipidemia                                                        | logBB = -0.038 (low) | ![Structure](image3) | [136,137]  |
| Compound 2p  | EC50 = 0.035 µM  | EC50 = 2.0 µM    | Inverse agonist   | cLogP = 7.27 | TPSA = 59.8   | N/A | DIO C57BL/6 mice | Lowers plasma glucose levels                                                                                                              | 0.05              | ![Structure](image4) | [148]         |
| Compound 8c  | Ki = 8.82 nM      | Ki = 1545 nM     | Inverse agonist   | N/A         | TPSA = 76     | N/A | N/A           | N/A                                                                                                                                   | 0.15              | ![Structure](image5) | [151]         |
| TXX522       | IC50 = 10.33 nmol/L | IC50 > 10 µmol/L | Neutral antagonist | LogP = 7.95 | TPSA = 56.73  | 1   | DIO C57BL/6 mice | Reduces body weight and fat mass, decreases metabolic complications                                                                       | 0.02 (Kp)         | ![Structure](image6) | [149]         |
| Compound 6a  | EC50 = 0.0082 µM | EC50 > 10 µM     | Inverse agonist   | cLogP = 6.15 | TPSA = 86.9   | 2   | DIO C57BL/6 mice | Reduces body weight, food intake, insulin level, liver fat, and cholesterol                                                              | 0.027             | ![Structure](image7) | [147]         |
Table 1. Cont.

| Compound | CB₁R Ki/EC₅₀/IC₅₀ | CB₂R Ki/EC₅₀/IC₅₀ | Nature of Compound | cLogP/LogP | TPSA/PSA (Å²) | HBD | Animal Model | Efficacy | Brain/Plasma Ratio | Structure | Ref. |
|----------|--------------------|--------------------|--------------------|-------------|--------------|------|--------------|---------|---------------------|-----------|-----|
| Compound 65 | Ki = 4.0 nM | Ki > 10,000 nM | Inverse agonist | N/A | N/A | N/A | N/A | N/A | 0.18 | Reduces hyperglycemia, dyslipidemia, hepatic steatosis, energy expenditure, and insulin resistance | ![Structure](https://example.com/structure65.png) | [152] |
| AJ5018 | IC₅₀ = 90.4 nM | N/A | Antagonist | N/A | N/A | N/A | DIO C57BL/6 and db/db mice | Reduces weight, increases energy expenditure; improves metabolic abnormalities, glycemic control, and insulin sensitivity | 0.1 | ![Structure](https://example.com/structureAJ5018.png) | [153] |
| AJ5012 | N/A | N/A | Antagonist | AlogP = 5.328 | PSA = 84.836 | N/A | DIO C57BL/6 and db/db mice | Reduces weight, increases energy expenditure; improves metabolic abnormalities, glycemic control, and insulin sensitivity | 0.2 | ![Structure](https://example.com/structureAJ5012.png) | [154] |
| Compound 17a | Ki = 47.1 nM | Ki = 20,000 nM | Antagonist | N/A | TPSA = 79 | Sprague Dawley rats | N/A | 0.0320 | ![Structure](https://example.com/structure17a.png) | [155] |
| Compound 18a | Ki = 2.9 nM | Ki = 2510 nM | Antagonist | N/A | TPSA = 76 | Sprague Dawley rats | N/A | 0.0214 | ![Structure](https://example.com/structure18a.png) | [155] |
Table 1. Cont.

| Compound | CB₁R  
| Kᵢ/EC₅₀/IC₅₀ | CB₂R  
| Kᵢ/EC₅₀/IC₅₀ | Nature of Compound | cLogP/LogP | TPSA/PSA (Å²) | HBD | Animal Model | Efficacy | Brain/Plasma Ratio | Structure | Ref. |
|----------|---------------|---------------|---------------|----------------|----------------|----------------|----------------|------------|----------------------|-----------|------|
| **Compound 18f** | | | | Antagonist | N/A | TPSA = 79 | Sprague Dawley rats | N/A | 0.379 | ![Structure](image) | [155] |
| ENV-2 | N/A | N/A | Antagonist | N/A | N/A | N/A | Wistar rats | Reduces glycemia and dyslipidemia | N/A | ![Structure](image) | [156] |
| MJ08 | Ki = 25.4 nM | IC₉₀ = 99.9 nmol/L | N/A | Inverse agonist | N/A | N/A | N/A | Wistar rats, DIO C57BL/6 mice | Stimulates hepatic glucose production | N/A | ![Structure](image) | [157,158] |
| PISMR | Ki = 57 nM | N/A | Antagonist | N/A | N/A | N/A | DIO C57Bl/6 mice | Reduces weight, food intake, and adiposity as well as improving glycemic control and lipid homeostasis | 0.24 | ![Structure](image) | [159,160] |

Half maximal effective concentration (EC₅₀); Half maximal inhibitory concentration (IC₉₀); Cannabinoid type-2 receptor (CB₂R); Calculated Log P (cLogP); Topological polar surface area/Polar surface area (TPSA/PSA); Hydrogen bond donor (HBD); Not available (N/A); Diet-induced obese (DIO); Apparent brain uptake clearance (CLapp); Ratio of the steady-state concentrations of the drug molecule in the brain and in the blood, expressed as log (Cₐblood/Cₐbrain); Brain to plasma distribution ratio (Kp); Atom-based Log P (ALogP).
6. Concluding Remarks

The appetite-stimulating ‘side effect’ of marijuana has been recognized for centuries. Mounting evidence supports the key role that CB₁Rs play in orexigenic signaling via central modulation of energy balance and feeding behavior. However, the influence of the eCB/CB₁R system on energy utilization and homeostasis cannot be solely explained by central mechanisms. Indeed, data show that this system also acts peripherally to modulate adipose tissue metabolism, kidney function, hepatic lipogenesis, muscle activity, and pancreatic homeostasis. Being tonically overactivated during obesity, the eCB/CB₁R system contributes to impairment in hormonal/metabolic function, propelling CB₁R forward as a potential therapeutic target for obesity. Whereas the globally acting CB₁R blocker rimonabant once held tremendous promise in ameliorating the metabolic abnormalities of obesity, its CNS-mediated adverse effects limited its clinical use. Targeting the eCB system using novel compounds that block CB₁Rs in periphery with negligible brain penetration still holds promise for future therapy for obesity and its sequelae.

Author Contributions: S.H. and J.T. wrote the manuscript.

Funding: This review article was made possible by the financial support provided by the ERC-2015-StG grant (8676841) to J.T.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Pollio, A. The Name of Cannabis: A Short Guide for Nonbotanists. Cannabis Cannabinoid Res. 2016, 1, 234–238. [CrossRef]
2. McPartland, J.M. Cannabis Systematics at the Levels of Family, Genus, and Species. Cannabis Cannabinoid Res. 2018, 3, 203–212. [CrossRef] [PubMed]
3. Pacher, P.; Batkai, S.; Kunos, G. The endocannabinoid system as an emerging target of pharmacotherapy. Pharmacol. Rev. 2006, 58, 389–462. [CrossRef] [PubMed]
4. Hanus, L.O.; Meyer, S.M.; Munoz, E.; Tagliatela-Scafati, O.; Appendino, G. Phytocannabinoids: A unified critical inventory. Nat. Prod. Rep. 2016, 33, 1357–1392. [CrossRef] [PubMed]
5. Berman, P.; Futoran, K.; Lewitus, G.M.; Mukha, D.; Benami, M.; Shlomi, T.; Meiri, D. A new ESI-LC/MS approach for comprehensive metabolic profiling of phytocannabinoids in Cannabis. Sci. Rep. 2018, 8, 14280. [CrossRef]
6. Wood, T.B.; Spivey, W.T.N.; Easterfield, T.H. Cannabinol. Part I. J. Chem. Soc. 1899, 75, 20–36. [CrossRef]
7. Hanus, L.O. Pharmacological and therapeutic secrets of plant and brain (endo)cannabinoids. Med. Res. Rev. 2009, 29, 213–271. [CrossRef] [PubMed]
8. Mechoulam, R.; Shvo, Y. Hashish, I. The structure of cannabidiol. Tetrahedron 1963, 19, 2073–2078. [CrossRef]
9. Gaoni, Y.; Mechoulam, R. Isolation, structure, partial, synthesis of an active constituent of hashish. J. Am. Chem. Soc. 1964, 86, 1646–1647. [CrossRef]
10. Mechoulam, R.; Gaoni, Y. The absolute configuration of delta-1-tetrahydrocannabinol, the major active constituent of hashish. Tetrahedron Lett. 1967, 12, 1109–1111. [CrossRef]
11. HIVELY, R.L.; MOSHER, W.A.; HOFFMANN, F.W. Isolation of trans-delta-tetrahydrocannabinol from marijuana. J. Am. Chem. Soc. 1966, 88, 1832–1833. [CrossRef] [PubMed]
12. Gaoni, Y.; Mechoulam, R. The structure and synthesis of cannabigerol, a new hashish constituent. Proc. Chem. Soc. 1964, 82. [CrossRef]
13. Gaoni, Y.; Mechoulam, R. Cannabichromene, a new active principle in hashish. Chem. Commun. 1966, 1, 20–21. [CrossRef]
14. Crombie, L.; Ponsford, R.; Shani, A.; Yagnitinsky, B.; Mechoulam, R. Hashish components. Photochemical production of cannabicyclol from cannabichromene. Tetrahedron Lett. 1968, 5771–5772. [CrossRef]
15. Devane, W.A.; Dysarz, F.A., 3rd.; Johnson, M.R.; Melvin, L.S.; Howlett, A.C. Determination and characterization of a cannabinoid receptor in rat brain. Mol. Pharmacol. 1988, 34, 605–613.
16. Matsuda, L.A.; Lollat, S.J.; Brownstein, M.J.; Young, A.C.; Bonner, T.I. Structure of a cannabinoid receptor and functional expression of the cloned cDNA. Nature 1990, 346, 561–564. [CrossRef] [PubMed]
17. Munro, S.; Thomas, K.L.; Abu-Shaar, M. Molecular characterization of a peripheral receptor for cannabinoids. *Nature* **1993**, *365*, 61–65. [CrossRef] [PubMed]

18. Hua, T.; Vemuri, K.; Nikas, S.P.; Laprairie, R.B.; Wu, Y.; Qu, L.; Pu, M.; Korde, A.; Jiang, S.; Ho, J.H.; et al. Crystal structures of agonist-bound human cannabinoid receptor CB1. *Nature* **2017**, *547*, 468–471. [CrossRef] [PubMed]

19. Shao, Z.; Yin, J.; Chapman, K.; Grzemska, M.; Clark, L.; Wang, J.; Rosenbaum, D.M. High-resolution crystal structure of the human CB1 cannabinoid receptor. *Nature* **2016**, *540*, 602–606. [CrossRef] [PubMed]

20. Hua, T.; Vemuri, K.; Pu, M.; Qu, L.; Wu, Y.; Zhao, S.; Shui, W.; Li, S.; Korde, A.; et al. Crystal Structure of the Human Cannabinoid Receptor CB1. *Cell* **2016**, *167*, 750–762. [CrossRef] [PubMed]

21. Li, X.; Hua, T.; Vemuri, K.; Ho, J.H.; Wu, Y.; Wu, L.; Popov, P.; Benchama, O.; Zvonok, N.; Locke, K.; et al. Crystal Structure of the Human Cannabinoid Receptor CB2. *Cell* **2019**, *176*, 459–467. [CrossRef] [PubMed]

22. Howlett, A.C. Cannabinoid receptor signaling. *Handb. Exp. Pharmacol.* **2005**, *168*, 53–79.

23. Mackie, K. Distribution of cannabinoid receptors in the central and peripheral nervous system. *Handb. Exp. Pharmacol.* **2005**, *168*, 299–325.

24. Tam, J.; Hinden, L.; Drori, A.; Udi, S.; Azar, S.; Baraghithy, S. The therapeutic potential of targeting the peripheral endocannabinoid/CB1 receptor system. *Eur. J. Intern. Med.* **2018**, *49*, 23–29. [CrossRef]

25. Zou, S.; Kumar, U. Cannabinoid Receptors and the Endocannabinoid System: Signaling and Function in the Central Nervous System. *Int. J. Mol. Sci.* **2018**, *19*, 833. [CrossRef]

26. Di Marzo, V.; Piscitelli, F. The Endocannabinoid System and its Modulation by Phytocannabinoids. *Neurotherapeutics* **2015**, *12*, 692–698. [CrossRef] [PubMed]

27. Devane, W.A.; Hanus, L.; Breuer, A.; Pertwee, R.G.; Stevenson, L.A.; Griffin, G.; Gibson, D.; Mandelbaum, A.; Etinger, A.; Mechoulam, R. Isolation and structure of a brain constituent that binds to the cannabinoid receptor. *Science* **1992**, *258*, 1946–1949. [CrossRef]

28. Sugiuara, T.; Kondo, S.; Sukagawa, A.; Nakane, S.; Shinoda, A.; Itoh, K.; Yamashita, A.; Waku, K. 2-Arachidonoylglycerol: A possible endogenous cannabinoid receptor ligand in brain. *Biochem. Biophys. Res. Commun.* **1995**, *215*, 89–97. [CrossRef]

29. Mechoulam, R.; Ben-Shabat, S.; Hanus, L.; Ligumsky, M.; Kaminski, N.E.; Schatz, A.R.; Gopher, A.; Almog, S.; Martin, B.R.; Compton, D.R.; et al. Identification of an endogenous 2-monoglyceride, present in canine gut, that binds to cannabinoid receptors. *Biochem. Pharmacol.* **1995**, *50*, 83–90. [CrossRef]

30. Pertwee, R.G.; Howlett, A.C.; Abood, M.E.; Alexander, S.P.; Di Marzo, V.; Elphick, M.R.; Greasley, P.J.; Hansen, H.S.; Kunos, G.; Mackie, K.; et al. International Union of Basic and Clinical Pharmacology. LXXIX. Cannabinoid receptors and their ligands: Beyond CB(1) and CB(2). *Pharmacol. Rev.* **2010**, *62*, 588–631. [CrossRef]

31. Di Marzo, V.; De Petrocellis, L. Why do cannabinoid receptors have more than one endogenous ligand? *Philos. Trans. R. Soc. Lond. B Biol. Sci.* **2012**, *367*, 3216–3228. [CrossRef] [PubMed]

32. Murataeva, N.; Straiker, A.; Mackie, K. Parsing the players: 2-arachidonoylglycerol synthesis and degradation in the CNS. *Br. J. Pharmacol.* **2014**, *171*, 1379–1391. [CrossRef] [PubMed]

33. McKinney, M.K.; Cravatt, B.F. Structure and function of fatty acid amide hydrolase. *Ann. Rev. Biochem.* **2005**, *74*, 411–432. [CrossRef] [PubMed]

34. Dinh, T.P.; Carpenter, D.; Leslie, F.M.; Freund, T.F.; Katona, I.; Sensi, S.L.; Kathuria, S.; Piomelli, D. Brain monoglyceride lipase participating in endocannabinoid inactivation. *Proc. Natl. Acad. Sci. USA* **2002**, *99*, 10819–10824. [CrossRef]

35. Di Marzo, V. ‘Endocannabinoids’ and other fatty acid derivatives with cannabimimetic properties: Biochemistry and possible physiopathological relevance. *Biochim. Biophys. Acta* **1998**, *1392*, 153–175. [CrossRef]

36. McPartland, J.M.; Guy, G.W.; Di Marzo, V. Care and feeding of the endocannabinoid system: A systematic review of potential clinical interventions that upregulate the endocannabinoid system. *PLoS ONE* **2014**, *9*, e89566. [CrossRef]

37. Aran, A.; Eylon, M.; Harel, M.; Polianski, L.; Nemirovski, A.; Tepper, S.; Schnapp, A.; Cassuto, H.; Wattad, N.; Tam, J. Lower circulating endocannabinoid levels in children with autism spectrum disorder. *Mol. Autism* **2019**, *10*, 2. [CrossRef]
38. Russo, E.B. Clinical endocannabinoid deficiency (CECD): Can this concept explain therapeutic benefits of cannabis in migraine, fibromyalgia, irritable bowel syndrome and other treatment-resistant conditions? *Neuro Endocrinol. Lett.* 2004, 25, 31–39.

39. Nieters, M.; Overdyk, F.; Smith, T.; Aarts, L.; Dahan, A. Opioid-induced respiratory depression in paediatrics: A review of case reports. *Br. J. Anaesth.* 2013, 110, 175–182. [CrossRef] [PubMed]

40. Wilson, K.C.; Saukkonen, J.J. Acute respiratory failure from abused substances. *Clin. Toxicol.* 1991, 29, 183–193. [CrossRef] [PubMed]

41. Wilson, M.M.; Philpot, C.; Morley, J.E. Anorexia of aging in long term care: Is dronabinol an effective appetite stimulant?—A pilot study. *J. Nutr. Health Aging* 2007, 11, 195–198.

42. May, C.N.; Ham, I.W.; Huslop, K.E.; Stone, F.A.; Mathias, C.J. Intravenous morphine causes hypertension, hyperglycaemia and increases sympatho-adrenal outflow in conscious rabbits. *Clin. Sci. (Lond.)* 1988, 75, 71–77. [CrossRef] [PubMed]

43. Sachs, J.; McGlade, E.; Yurgelun-Todd, D. Safety and Toxicology of Cannabinoids. *Neurotherapeutics* 2015, 12, 735–746. [CrossRef]

44. Adams, I.B.; Martin, B.R. Cannabis: Pharmacology and toxicology in animals and humans. *Addiction* 1996, 91, 1585–1614. [CrossRef]

45. Beal, J.E.; Olson, R.; Laubenstein, L.; Morales, J.O.; Bellman, P.; Yangco, B.; Lefkowitz, L.; Plasse, T.F.; Grotenhermen, F.; Frystyk, J.; Flyvbjerg, A.; Stoving, R.K.; Dronabinol in severe, enduring anorexia nervosa: A randomized controlled trial. *Int. J. Eat. Disord.* 2014, 47, 18–23. [CrossRef] [PubMed]

46. Reece, A.S. Chronic toxicology of cannabis. *Clin. Toxicol.* 2009, 47, 517–524. [CrossRef] [PubMed]

47. Herkenham, M.; Lynn, A.B.; Johnson, M.R.; Melvin, L.S.; de Costa, B.R.; Rice, K.C. Characterization and localization of cannabinoid receptors in rat brain: A quantitative in vitro autoradiographic study. *J. Neurosci.* 1991, 11, 563–583. [CrossRef]

48. Simon, V.; Cota, D. Mechanisms in Endocrinology: Endocannabinoids and metabolism: Past, present and future. *Eur. J. Endocrinol.* 2017, 176, R309–R324. [CrossRef]

49. Foltin, R.W.; Brady, J.V.; Fischman, M.W. Behavioral analysis of marijuana effects on food intake in humans. *Pharmacol. Biochem. Behav.* 1986, 25, 577–582. [CrossRef]

50. Hollister, L.E. Hunger and appetite after single doses of marihuana, alcohol, and dextroamphetamine. *Clin. Pharmacol. Ther.* 1971, 12, 44–49. [CrossRef]

51. Abel, E.L. Effects of marihuana on the solution of anagrams, memory and appetite. *Nature* 1971, 231, 260–261. [CrossRef] [PubMed]

52. Di Marzo, V.; Ligresti, A.; Cristiano, L. The endocannabinoid system as a link between homoeostatic and hedonic pathways involved in energy balance regulation. *Int. J. Obes. (Lond.)* 2009, 33 (Suppl. 2), S18–S24. [CrossRef] [PubMed]

53. Machado Rocha, F.C.; Stefano, S.C.; De Cassia Haiek, R.; Rosa Oliveira, L.M.; Da Silveira, D.X. Therapeutic use of Cannabis sativa on chemotherapy-induced nausea and vomiting among cancer patients: Systematic review and meta-analysis. *Eur. J. Cancer Care (Engl.)* 2008, 17, 431–443. [CrossRef] [PubMed]

54. Badowski, M.E.; Yanful, P.K. Dronabinol oral solution in the management of anorexia and weight loss in AIDS and cancer. *Ther. Clin. Risk Manag.* 2018, 14, 643–651. [CrossRef] [PubMed]

55. Plassie, T.F.; Gorter, R.W.; Krasnow, S.H.; Lane, M.; Shepard, K.V.; Wadleigh, R.G. Recent clinical experience with dronabinol. *Pharmacol. Biochem. Behav.* 1991, 40, 695–700. [CrossRef]

56. Struwe, M.; Kämper, S.H.; Geiger, C.J.; Pavia, A.T.; Plassie, T.F.; Shepard, K.V.; Ries, K.; Evans, T.G. Effect of dronabinol on nutritional status in HIV infection. *Ann. Pharmacother.* 1993, 27, 827–831. [CrossRef] [PubMed]

57. Beal, J.E.; Olson, R.; Laubenstein, L.; Morales, J.O.; Bellman, P.; Yangco, B.; Lefkowitz, L.; Plassie, T.F.; Shepard, K.V. Dronabinol as a treatment for anorexia associated with weight loss in patients with AIDS. *J. Pain Symptom Manag.* 1995, 10, 89–97. [CrossRef]

58. Andries, A.; Frystyk, J.; Flyvbjerg, A.; Stoving, R.K. Dronabinol in severe, enduring anorexia nervosa: A randomized controlled trial. *Int. J. Eat. Disord.* 2014, 47, 18–23. [CrossRef] [PubMed]

59. Wolfer, L.; Stelly, M.; Morris, J.; McLaughlin, J.; Wolfer, B.J. Effects of dronabinol on anorexia and disturbed behavior in patients with Alzheimer’s disease. *Int. J. Geriatr. Psychiatry* 1997, 12, 913–919. [CrossRef]

60. Wilson, M.M.; Philpot, C.; Morley, J.E. Anorexia of aging in long term care: Is dronabinol an effective appetite stimulant?—A pilot study. *J. Nutr. Health Aging* 2007, 11, 195–198.
61. Wiley, J.L.; Burston, J.J.; Leggett, D.C.; Alekseeva, O.O.; Razdan, R.K.; Mahadevan, A.; Martin, B.R. CB1 cannabinoid receptor-mediated modulation of food intake in mice. *Br. J. Pharmacol.* 2005, 145, 293–300. [CrossRef] [PubMed]

62. McLaughlin, C.L.; Baile, C.A.; Bender, P.E. Cannabinoids and feeding in sheep. *Psychopharmacology* 1979, 64, 321–323. [CrossRef] [PubMed]

63. Gallate, J.E.; Saharov, T.; Mallet, P.E.; McGregor, I.S. Increased motivation for beer in rats following administration of a cannabinoid CB1 receptor agonist. *Eur. J. Pharmacol.* 1999, 370, 233–240. [CrossRef] [PubMed]

64. Brown, J.E.; Kassouny, M.; Cross, J.K. Kinetic studies of food intake and sucrose solution preference by rats treated with low doses of delta-9-tetrahydrocannabinol. *Behav. Biol.* 1977, 20, 104–110. [CrossRef]

65. Trojniar, W.; Wise, R.A. Facilitatory effect of delta-9-tetrahydrocannabinol on hypothalamically induced feeding. *Psychopharmacology* 1991, 130, 172–176. [CrossRef]

66. Hao, S.; Avraham, Y.; Mechoulam, R.; Berry, E.M. Low dose anandamide affects food intake, cognitive function, neurotransmitter and corticosterone levels in diet-restricted mice. *Eur. J. Pharmacol.* 2000, 392, 147–156. [CrossRef]

67. Williams, C.M.; Kirkham, T.C. Observational analysis of feeding induced by Delta9-THC and anandamide. *Physiol. Behav.* 2002, 76, 241–250. [CrossRef]

68. Williams, C.M.; Kirkham, T.C. Anandamide induces overeating: Mediation by central cannabinoid (CB1) receptors. *Psychopharmacology* 1999, 143, 315–317. [CrossRef]

69. Jamshidi, N.; Taylor, D.A. Anandamide administration into the ventromedial hypothalamus stimulates appetite in rats. *Br. J. Pharmacol.* 2001, 134, 1151–1154. [CrossRef]

70. Gallate, J.E.; Saharov, T.; Mallet, P.E.; McGregor, I.S. Increased motivation for beer in rats following administration of a cannabinoid CB1 receptor agonist. *Eur. J. Pharmacol.* 1999, 370, 233–240. [CrossRef] [PubMed]

71. Kirkham, T.C.; Williams, C.M.; Fezza, F.; Di Marzo, V. Endocannabinoid levels in rat limbic forebrain and hypothalamus in relation to fasting, feeding and satiation: Stimulation of eating by 2-arachidonoylglycerol. *Br. J. Pharmacol.* 2002, 136, 550–557. [CrossRef] [PubMed]

72. Gagnon, M.A.; Elie, R. Effects on hunger and thirst. *Behav. Biol.* 1975, 104, 914–921. [PubMed]

73. Chopra, R.N.; Chopra, G.S. The Present Position of Hemp-Drug Addiction in India. *Indian Med. Res. Mem.* 1939, 31, 1–119. [CrossRef]

74. Bouquet, J. Cannabis. *Bull. Nurc.* 1951, 3, 22–45.

75. Abel, E.L. Cannabis: Effects on hunger and thirst. *Behav. Biol.* 1975, 15, 255–281. [CrossRef]

76. Clark, T.M.; Jones, J.M.; Hall, A.G.; Tabner, S.A.; Kmiec, R.L. Theoretical Explanation for Reduced Body Mass Index and Obesity Rates in Cannabis Users. *Cannabis Cannabinoid Res.* 2018, 3, 259–271. [CrossRef] [PubMed]

77. Ceccarini, J.; Kuepper, R.; Kemels, D.; van Os, J.; Henquet, C.; Van Laere, K. [18F]MK-9470 PET measurement of cannabinoid CB1 receptor availability in chronic cannabis users. *Add. Biol.* 2015, 20, 357–367. [CrossRef] [PubMed]

78. D’Souza, D.C.; Cortes-Briones, J.A.; Ranganathan, M.; Thurnauer, H.; Creatura, G.; Surti, T.; Planeta, B.; Neumeister, A.; Pittman, B.; Normandin, M.; et al. Rapid Changes in CB1 Receptor Availability in Cannabis Dependent Males after Abstinence from Cannabis. *Biol. Psychiatry Cogn. Neurosci. Neuroimaging* 2016, 1, 60–67. [CrossRef]

79. Hirvonen, J.; Goodwin, R.S.; Li, C.T.; Terry, G.E.; Zoghbi, S.S.; Morse, C.; Pike, V.W.; Volkow, N.D.; Huestis, M.A.; Innis, R.B. Reversible and regionally selective downregulation of brain cannabinoid CB1 receptors in chronic daily cannabis smokers. *Mol. Psychiatry* 2012, 17, 642–649. [CrossRef]

80. Colombo, G.; Agabio, R.; Diaz, G.; Lobina, C.; Reali, R.; Gessa, G.L. Appetite suppression and weight loss after the cannabinoid antagonist SR 141716. *Life Sci.* 1998, 63, PL113–PL117. [CrossRef] [PubMed]

81. Arnone, M.; Maruani, J.; Chaperon, E.; Thiebot, M.H.; Poncelet, M.; Soubrie, P.; Le Fur, G. Selective inhibition of sucrose and ethanol intake by SR 141716, an antagonist of central cannabinoid (CB1) receptors. *Psychopharmacology* 1997, 132, 104–106. [CrossRef] [PubMed]

82. Ravinet Trillou, C.; Arnone, M.; Delgorge, C.; Gonalons, N.; Keane, P.; Maffrand, J.P.; Soubrie, P. Anti-obesity effect of SR141716, a CB1 receptor antagonist, in diet-induced obese mice. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 2003, 284, R345–353. [CrossRef] [PubMed]

83. Simian, J.; Keane, M.; Keane, P.E.; Soubrie, P. SR 141716, a CB1 cannabinoid receptor antagonist, selectively reduces sweet food intake in marmoset. *Behav. Pharmacol.* 1998, 9, 179–181. [PubMed]
84. Freedland, C.S.; Poston, J.S.; Porrino, L.J. Effects of SR141716A, a central cannabinoid receptor antagonist, on food-maintained responding. Pharmacol. Biochem. Behav. 2000, 67, 265–270. [CrossRef]

85. Ward, S.J.; Dykstra, L.A. The role of CB1 receptors in sweet versus fat reinforcement: Effect of CB1 receptor deletion, CB1 receptor antagonism (SR141716A) and CB1 receptor agonism (CP-55940). Behav. Pharmacol. 2005, 16, 381–388. [CrossRef]

86. Cota, D.; Marsicano, G.; Tschop, M.; Grubler, Y.; Flachskamm, C.; Schubert, M.; Auer, D.; Yassouridis, A.; Thone-Reineke, C.; Ortmann, S.; et al. The endogenous cannabinoid system affects energy balance via central orexigenic drive and peripheral lipogenesis. J. Clin. Investig. 2003, 112, 423–431. [CrossRef]

87. Despres, J.P.; Golay, A.; Sjostrom, L. Rimonabant in Obesity-Lipids Study Group. Effects of rimonabant on metabolic risk factors in overweight patients with dyslipidemia. N. Engl. J. Med. 2005, 353, 2121–2134. [CrossRef]

88. Pi-Sunyer, F.X.; Aronne, L.J.; Heshmati, H.M.; Devin, J.; Rosenstock, J.; RIO-North America Study Group. Effect of rimonabant, a cannabinoid-1 receptor blocker, on weight and cardiometabolic risk factors in overweight or obese patients: RIO-North America: A randomized controlled trial. JAMA 2006, 295, 761–775. [CrossRef]

89. Van Gaal, L.F.; Rissanen, A.M.; Scheen, A.J.; Ziegler, O.; Rossner, S.; Group, R.I.-E.S. Effects of the cannabinoid-1 receptor blocker rimonabant on weight reduction and cardiovascular risk factors in overweight patients: 1-year experience from the RIO-Europe study. Lancet 2005, 365, 1389–1397. [CrossRef]

90. Scheen, A.J.; Finer, N.; Hollander, P.; Jensen, M.D.; Van Gaal, L.F. Efficacy and tolerability of rimonabant in overweight or obese patients with type 2 diabetes: A randomised controlled study. Lancet 2006, 368, 1660–1672. [CrossRef]

91. Despres, J.P.; Ross, R.; Boka, G.; Almeras, N.; Lemieux, I.; ADAGIO-Lipids Investigators. Effect of rimonabant on the high-triglyceride/low-HDL-cholesterol dyslipidemia, intraabdominal adiposity, and liver fat: The ADAGIO-Lipids trial. Arterioscler. Thromb. Vasc. Biol. 2009, 29, 416–423. [CrossRef] [PubMed]

92. Rosenstock, J.; Hollander, P.; Chevalier, S.; Iranmanesh, A.; SERENADE: The Study Evaluating Rimonabant Efficacy in Drug-naive Diabetic Patients: Effects of monotherapy with rimonabant, the first selective CB1 receptor antagonist, on glycemic control, body weight, and lipid profile in drug-naive type 2 diabetes. Diabetes Care 2008, 31, 2169–2176. [CrossRef] [PubMed]

93. Hollander, F.A.; Amod, A.; Litwak, L.E.; Chaudhari, U. Effect of rimonabant on glycemic control in insulin-treated type 2 diabetes: The ARPEGGIO trial. Diabetes Care 2010, 33, 605–607. [CrossRef] [PubMed]

94. Christensen, R.; Kristensen, P.K.; Bartels, E.M.; Bliddal, H.; Astrup, A. Efficacy and safety of the weight-loss drug rimonabant: A meta-analysis of randomised trials. Lancet 2007, 370, 1706–1713. [CrossRef]

95. Jones, D. End of the line for cannabinoid receptor 1 as an anti-obesity target? Nat. Rev. Drug Discov. 2008, 7, 961–962. [CrossRef] [PubMed]

96. Gomez, R.; Navarro, M.; Ferrer, B.; Trigo, J.M.; Bilbao, A.; Del Arco, I.; Cippitelli, A.; Nava, F.; Piomelli, D.; Rodriguez de Fonseca, F. A peripheral mechanism for CB1 cannabinoid receptor-dependent modulation of feeding. J. Neurosci. 2002, 22, 9612–9617. [CrossRef]

97. Bensaid, M.; Gary-Bobo, M.; Esclangon, A.; Maffrand, J.P.; Le Fur, G.; Oury-Donat, F.; Soubrie, P. The cannabinoid CB1 receptor antagonist SR141716 increases Acrp30 mRNA expression in adipose tissue of obese fa/fa rats and in cultured adipocyte cells. Mol. Pharmacol. 2003, 63, 908–914. [CrossRef]

98. Jourdan, T.; Djaouti, L.; Demizieux, L.; Cresti, J.; Vergees, B.; Degrace, P. CB1 antagonism exerts specific molecular effects on visceral and subcutaneous fat and reverses liver steatosis in diet-induced obese mice. Diabetes 2010, 59, 926–934. [CrossRef] [PubMed]

99. Quarta, C.; Bellochcio, L.; Mancini, G.; Mazza, R.; Cervino, C.; Braulke, L.F.; Fekete, C.; Latorre, R.; Nanni, C.; Bucci, M.; et al. CB(1) signaling in forebrain and sympathetic neurons is a key determinant of endocannabinoid actions on energy balance. Cell Metab. 2010, 11, 273–285. [CrossRef]

100. Osei-Hyiaman, D.; Liu, J.; Zhou, L.; Godlewski, G.; Harvey-White, J.; Jeong, W.I.; Batkai, S.; Marsicano, G.; Lutz, B.; Buettner, C.; et al. Hepatic CB1 receptor is required for development of diet-induced steatosis, dyslipidemia, and insulin and leptin resistance in mice. J. Clin. Investig. 2008, 118, 3160–3169. [CrossRef] [PubMed]

101. Pagotto, U.; Marsicano, G.; Cota, D.; Lutz, B.; Pasquali, R. The emerging role of the endocannabinoid system in endocrine regulation and energy balance. Endocr. Rev. 2006, 27, 73–100. [CrossRef] [PubMed]
102. Udi, S.; Hinden, L.; Earley, B.; Drori, A.; Reuveni, N.; Hadar, R.; Cinar, R.; Nemirovski, A.; Tam, J. Proximal Tubular Cannabinoid-1 Receptor Regulates Obesity-Induced CKD. *J. Am. Soc. Nephrol.* 2017, 28, 3518–3532. [CrossRef]

103. Jourdan, T.; Godlewski, G.; Cinar, R.; Bertola, A.; Szanda, G.; Liu, J.; Tam, J.; Han, T.; Mukhopadhyay, B.; Skarulis, M.C.; et al. Activation of the Nlrp3 inflammasome in infiltrating macrophages by endocannabinoids mediates beta cell loss in type 2 diabetes. *Nat. Med.* 2013, 19, 1132–1140. [CrossRef]

104. Bordicchia, M.; Battistoni, I.; Mancinelli, L.; Giannini, E.; Refi, G.; Minardi, D.; Muzzonigro, G.; Mazzucchelli, R.; Montironi, R.; Piscitelli, F.; et al. Cannabinoid CB1 receptor expression in relation to visceral adipose depots, endocannabinoid levels, microvascular damage, and the presence of the Cnr1 A3813G variant in humans. *Metabolism* 2010, 59, 734–741. [CrossRef]

105. Engeli, S.; Bohnke, J.; Feldpauscher, M.; Gorzelniak, K.; Janke, J.; Batkai, S.; Pacher, P.; Harvey-White, J.; Luft, F.C.; Sharma, A.M.; et al. Activation of the peripheral endocannabinoid system in human obesity. *Diabetes* 2005, 54, 2838–2843. [CrossRef] [PubMed]

106. Bluher, M.; Engeli, S.; Kloting, N.; Berndt, J.; Fasshauer, M.; Batkai, S.; Pacher, P.; Schon, M.R.; Jordan, J.; Stumvoll, M. Dysregulation of the peripheral and adipose tissue endocannabinoid system in human abdominal obesity. *Diabetes* 2006, 55, 3053–3060. [CrossRef] [PubMed]

107. Di Marzo, V.; Verrijken, A.; Hakkarainen, A.; Petrosino, S.; Mertens, I.; Lundbom, N.; Piscitelli, F.; Westerbacka, J.; Soro-Paavonen, A.; Matias, I.; et al. Role of insulin as a negative regulator of plasma endocannabinoid levels in obese and nonobese subjects. *Eur. J. Endocrinol.* 2009, 161, 715–722. [CrossRef] [PubMed]

108. Abdulnour, J.; Yasari, S.; Rabasa-Lhoret, R.; Faraj, M.; Petrosino, S.; Piscitelli, F.; Prud’homme, D.; Di Marzo, V. Circulating endocannabinoids in insulin sensitive vs. insulin resistant obese postmenopausal women. A MONET group study. *Obesity (Silver Spring)* 2014, 22, 211–216. [CrossRef] [PubMed]

109. Knani, I.; Earley, B.J.; Udi, S.; Nemirovski, A.; Hadar, R.; Gammal, A.; Cinar, R.; Hirsch, H.J.; Pollak, Y.; Gross, I.; et al. Targeting the endocannabinoid/CB1 receptor system for treating obesity in Prader-Willi syndrome. *Mol. Metab.* 2016, 5, 1187–1199. [CrossRef] [PubMed]

110. Azar, S.; Sherf-Dagan, S.; Nemirovski, A.; Webb, M.; Raziel, A.; Keidar, A.; Goitein, D.; Sakran, N.; Shibolet, O.; Tam, J.; et al. Circulating Endocannabinoids Are Reduced Following Bariatric Surgery and Associated with Improved Metabolic Homeostasis in Humans. *Obes. Surg.* 2019, 29, 268–276. [CrossRef]

111. Zelber-Sagi, S.; Azar, S.; Nemirovski, A.; Webb, M.; Halpern, Z.; Shibolet, O.; Tam, J. Serum levels of endocannabinoids are independently associated with nonalcoholic fatty liver disease. *Obesity* 2017, 25, 94–101. [CrossRef] [PubMed]

112. Ruiz de Azua, I.; Mancini, G.; Srivastava, R.K.; Rey, A.A.; Cardinal, P.; Tedesco, L.; Zingaretti, C.M.; Sassmann, A.; Quarta, C.; Schwitter, C.; et al. Adipocyte cannabinoid receptor CB1 regulates energy homeostasis and alternatively activated macrophages. *J. Clin. Investig.* 2017, 127, 4148–4162. [CrossRef]

113. Gonzalez-Mariscal, I.; Montoro, R.A.; Doyle, M.E.; Liu, Q.R.; Rouse, M.; O’Connell, J.F.; Santa-Cruz Calvo, S.; Krzysik-Walker, S.M.; Ghosh, S.; Carlson, O.D.; et al. Absence of cannabinoid 1 receptor in beta cells protects against high-fat/high-sugar diet-induced beta cell dysfunction and inflammation in murine islets. *Diabetologia* 2018, 61, 1470–1483. [CrossRef] [PubMed]

114. Gonzalez-Mariscal, I.; Montoro, R.A.; O’Connell, J.F.; Kim, Y.; Gonzalez-Freire, M.; Liu, Q.R.; Alfaras, I.; Carlson, O.D.; Lehrmann, E.; Zhang, Y.; et al. Muscle cannabinoid 1 receptor regulates Il-6 and myostatin expression, governing physical performance and whole-body metabolism. *FASEB J.* 2019. [CrossRef] [PubMed]

115. Drori, A.; Permyakova, A.; Hadar, R.; Udi, S.; Nemirovski, A.; Tam, J. Cannabinoid-1 receptor regulates mitochondrial dynamics and function in renal proximal tubular cells. *Diabetes Obes. Metab.* 2019, 21, 146–159. [CrossRef] [PubMed]

116. Hinden, L.; Udi, S.; Drori, A.; Gammal, A.; Nemirovski, A.; Hadar, R.; Baragihthy, S.; Permyakova, A.; Geron, M.; Cohen, M.; et al. Modulation of Renal GLUT2 by the Cannabinoid-1 Receptor: Implications for the Treatment of Diabetic Nephropathy. *J. Am. Soc. Nephrol.* JASN 2018, 29, 434–448. [CrossRef]

117. Wager, T.T.; Chandrasekaran, R.Y.; Hou, X.; Troutman, M.D.; Verhoest, P.R.; Villalobos, A.; Will, Y. Defining desirable central nervous system drug space through the alignment of molecular properties, in vitro ADME, and safety attributes. *ACS Chem. Neurosci.* 2010, 1, 420–434. [CrossRef]
Toxins 2019, 11, 275

118. Chorvat, R.J. Peripherally restricted CB1 receptor blockers. Bioorganic med. Chem. Lett. 2013, 23, 4751–4760. [CrossRef]
119. Sharma, M.K.; Murumkar, P.R.; Kanhd, A.M.; Giridhar, R.; Yadav, M.R. Prospective therapeutic agents for obesity: Molecular modification approaches of centrally and peripherally acting selective cannabinoid 1 receptor antagonists. Eur. J. Med. Chem. 2014, 79, 298–339. [CrossRef] [PubMed]
120. Sharma, M.K.; Murumkar, P.R.; Giridhar, R.; Yadav, M.R. Exploring structural requirements for peripherally acting 1,5-diaryl pyrazole-containing cannabinoid 1 receptor antagonists for the treatment of obesity. Mol. Divers. 2015, 19, 871–893. [CrossRef]
121. Yadav, M.R.; Murumkar, P.R. Advances in patented CB1 receptor antagonists for obesity. Pharm. Patent Anal. 2018, 7, 169–173. [CrossRef] [PubMed]
122. Tam, J.; Vemuri, V.K.; Liu, J.; Batkai, S.; Mukhopadhyay, B.; Godlewski, G.; Osei-Hyiaman, D.; Ohnuma, S.; Ambudkar, S.V.; Pickel, J.; et al. Peripheral CB1 cannabinoid receptor blockade improves cardiometabolic risk in mouse models of obesity. J. Clin. Invest. 2010, 120, 2953–2966. [CrossRef] [PubMed]
123. Cluny, N.L.; Vemuri, V.K.; Chambers, A.P.; Limebeer, C.L.; Bedard, H.; Wood, J.T.; Lutz, B.; Zimmer, A.; Parker, L.A.; Makiarianis, A.; et al. A novel peripherally restricted cannabinoid receptor antagonist, AM6545, reduces food intake and body weight, but does not cause malaise, in rodents. Br. J. Pharmacol. 2010, 161, 629–642. [CrossRef] [PubMed]
124. Argueta, D.A.; DiPatrizio, N.V. Peripheral endocannabinoid signaling controls hyperphagia in western diet-induced obesity. Physiol. Behav. 2017, 171, 32–39. [CrossRef] [PubMed]
125. Bowles, N.P.; Karatsoreos, I.N.; Li, X.; Vemuri, V.K.; Wood, J.A.; Li, Z.; Tamashiro, K.L.; Schwartz, G.J.; Makiarianis, A.M.; Kunos, G.; et al. A peripheral endocannabinoid mechanism contributes to glucocorticoid-mediated metabolic syndrome. Proc. Natl. Acad. Sci. USA 2015, 112, 285–290. [CrossRef]
126. Boon, M.R.; Kooijman, S.; van Dam, A.D.; Pelgrom, L.R.; Berbee, J.F.; Visseren, C.A.; van Aggele, R.C.; van den Hoek, A.M.; Sips, H.C.; Lombes, M.; et al. Peripheral cannabinoid 1 receptor blockade activates brown adipose tissue and diminishes dyslipidemia and obesity. FASEB J. 2014, 28, 5361–5375. [CrossRef] [PubMed]
127. Ma, H.; Zhang, G.; Mou, C.; Fu, X.; Chen, Y. Peripheral CB1 Receptor Neutral Antagonist, AM6545, Ameliorates Hypometabolic Obesity and Improves Adipokine Secretion in Monosodium Glutamate Induced Obese Mice. Front. Pharmacol. 2018, 9, 156. [CrossRef]
128. Tam, J.; Cinar, R.; Liu, J.; Godlewski, G.; Wesley, D.; Jourdan, T.; Szanda, G.; Mukhopadhyay, B.; Chedester, L.; Liow, J.S.; et al. Peripheral cannabinoid-1 receptor inverse agonism reduces obesity by reversing leptin resistance. Cell Metab. 2012, 16, 167–179. [CrossRef] [PubMed]
129. Tam, J.; Szanda, G.; Drori, A.; Liu, Z.; Cinar, R.; Kashiwaya, Y.; Reitman, M.L.; Kunos, G. Peripheral cannabinoid-1 receptor blockade restores hypothalamic leptin signaling. Mol. Metab. 2017, 6, 1113–1125. [CrossRef] [PubMed]
130. Klumpers, L.E.; Fridberg, M.; de Kam, M.L.; Little, P.B.; Jensen, N.O.; Kleinloog, H.D.; Elling, C.E.; van Gerven, J.M. Peripheral selectivity of the novel cannabinoid receptor antagonist TM38837 in healthy subjects. Br. J. Clin. Pharmacol. 2013, 76, 846–857. [CrossRef]
131. Takano, A.; Gulyas, B.; Varnas, K.; Little, P.B.; Noerregaard, P.K.; Jensen, N.O.; Elling, C.E.; Halldin, C. Low brain CB1 receptor occupancy by a second generation CB1 receptor antagonist TM38837 in comparison with rimonabant in nonhuman primates: A PET study. Synapse 2014, 68, 89–97. [CrossRef]
132. Hung, M.S.; Chang, C.P.; Li, T.C.; Yeh, T.K.; Song, J.S.; Lin, Y.; Wu, C.H.; Kuo, P.C.; Amancha, P.K.; Wong, Y.C.; et al. Discovery of 1-(2,4-dichlorophenyl)-4-ethyl-5-(5-(2-(4-(trifluoromethyl)phenyl)ethynyl)thiophene-2-yl)-N-(piperidin-1-yl)-1H-pyrazole-3-carboxamide as a potential peripheral cannabinoid-1 receptor inverse agonist. ChemMedChem 2010, 5, 1439–1443. [CrossRef]
133. Ward, S.J.; Raffa, R.B. Rimonabant redux and strategies to improve the future outlook of CB1 receptor neutral-agonist/inverse-agonist therapies. Obesity 2011, 19, 1325–1334. [CrossRef] [PubMed]
134. Noerregaard, P.K.; Fridberg, M.; Elling, C.E. TM38837—A novel second generation peripheral selective CB1 receptor antagonist with efficacy and potency in rodent obesity models equal to brain-penetrant CB1 antagonist rimonabant. In Proceedings of the 20th Annual Symposium of the International Cannabinoid Research Society, Lund, Sweden, 23–27 July 2010.
135. Hsiao, W.C.; Shia, K.S.; Wang, Y.T.; Yeh, Y.N.; Chang, C.P.; Lin, Y.; Chen, P.H.; Wu, C.H.; Chao, Y.S.; Hung, M.S. A novel peripheral cannabinoid receptor 1 antagonist, BPR0912, reduces weight independently of food intake and modulates thermogenesis. Diabetes Obes. Metab. 2015, 17, 495–504. [CrossRef]
Toxins 2019, 11, 275

136. Mastinu, A.; Pira, M.; Pinna, G.A.; Pisu, C.; Casu, M.A.; Reali, R.; Marcello, S.; Murineddu, G.; Lazzari, P. NNESS06SM reduces body weight with an improved profile relative to SR141716A. *Pharmacol. Res.* 2013, 74, 94–108. [CrossRef] [PubMed]

137. Lazzari, P.; Serra, V.; Marcello, S.; Pira, M.; Mastinu, A. Metabolic side effects induced by olanzapine treatment are neutralized by CB1 receptor antagonist compounds co-administration in female rats. *Eur. Neuropsychopharmacol.* 2017, 27, 667–678. [CrossRef] [PubMed]

138. Pavon, F.J.; Bilbao, A.; Hernandez-Folgado, L.; Cippitelli, A.; Jagerovic, N.; Abellan, G.; Rodriguez-Franco, M.A.; Serrano, A.; Macias, M.; Gomez, R.; et al. Antiobesity effects of the novel neutral cannabinoid receptor antagonist 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-3-hexyl-1H-1,2,4-triazole–LH 21. *Neuropharmacology* 2006, 51, 358–366. [CrossRef] [PubMed]

139. Pavon, F.J.; Serrano, A.; Perez-Valero, V.; Jagerovic, N.; Hernandez-Folgado, L.; Bermudez-Silva, F.J.; Macias, M.; Goya, P.; de Fonseca, F.R. Central versus peripheral antagonism of cannabinoid CB1 receptor in obesity: Effects of LH-21, a peripherally acting neutral cannabinoid receptor antagonist, in Zucker rats. *J. Neuroendocrinol.* 2008, 20 (Suppl. 1), 116–123. [CrossRef]

140. Alonso, M.; Serrano, A.; Vida, M.; Crespillo, A.; Hernandez-Folgado, L.; Jagerovic, N.; Goya, P.; Reyes-Cabello, C.; Perez-Valero, V.; Decara, J.; et al. Anti-obesity efficacy of LH-21, a cannabinoid CB1 receptor antagonist with poor brain penetration, in diet-induced obese rats. *Br. J. Pharmacol.* 2012, 165, 2274–2291. [CrossRef]

141. Chen, R.Z.; Frassetto, A.; Lao, J.Z.; Huang, R.R.; Xiao, J.C.; Clements, M.J.; Walsh, T.F.; Hale, J.J.; Wang, J.; Tong, X.; et al. Pharmacological evaluation of LH-21, a newly discovered molecule that binds to cannabinoid CB1 receptor. *Eur. J. Pharmacol.* 2008, 584, 338–342. [CrossRef] [PubMed]

142. LoVerme, J.; Duranti, A.; Tontini, A.; Spadoni, G.; Mor, M.; Rivara, S.; Stella, N.; Xu, C.; Tarzia, G.; Piomelli, D. Synthesis and characterization of a peripherally restricted CB1 cannabinoid antagonist, URB447, that reduces feeding and body-weight gain in mice. *Bioorganic Med. Chem. Lett.* 2009, 19, 639–643. [CrossRef]

143. DiPatrizio, N.V.; Astarita, G.; Schwartz, G.; Li, X.; Piomelli, D. Endocannabinoid signaling in the gut controls dietary fat intake. *Proc. Natl. Acad. Sci. USA* 2011, 108, 12904–12908. [CrossRef] [PubMed]

144. DiPatrizio, N.V.; Hoskin, A.; Jung, K.M.; Piomelli, D. Endocannabinoid signaling in the gut mediates preference for dietary unsaturated fats. *FASEB J.* 2013, 27, 2513–2520. [CrossRef]

145. Son, M.H.; Kim, H.D.; Chae, Y.; Kim, M.K.; Shin, C.Y.; Ahn, G.J.; Choi, S.H.; Yang, E.K.; Park, K.J.; Chae, H.W.; et al. Peripherally acting CB1-receptor antagonist: The relative importance of central and peripheral CB1 receptors in adiposity control. *Int. J. Obes.* 2010, 34, 547–556. [CrossRef] [PubMed]

146. Receveur, J.M.; Murray, A.; Linget, J.M.; Norregaard, P.K.; Cooper, M.; Bjurling, E.; Nielsen, P.A.; Hogberg, T. Conversion of 4-cyanomethyl-pyrazole-3-carboxamides into CB1 antagonists with lowered propensity to pass the blood-brain-barrier. *Bioorganic Med. Chem. Lett.* 2010, 20, 453–457. [CrossRef] [PubMed]

147. Zhang, Y.M.; Greco, M.N.; Macielag, M.J.; Teleha, C.A.; DesJarlais, R.L.; Tang, Y.; Ho, G.; Hou, C.; Chen, C.; Zhao, S.; et al. 6-Benzhydryl-4-amino-quinolin-2-ones as Potent Cannabinoid Type 1 (CB1) Receptor Inverse Agonists and Chemical Modifications for Peripheral Selectivity. *J. Med. Chem.* 2018, 61, 10276–10298. [CrossRef]

148. Matthews, J.M.; McNally, J.J.; Connolly, P.J.; Xia, M.; Zhu, B.; Black, S.; Chen, C.; Hou, C.; Liang, Y.; Tang, Y.; et al. Tetrahydroindazole derivatives as potent and peripherally selective cannabinoid-1 (CB1) receptor inverse agonists. *Bioorganic Med. Chem. Lett.* 2016, 26, 5346–5349. [CrossRef]

149. Chen, W.; Shui, F.; Liu, C.; Zhou, X.; Li, W.; Zheng, Z.; Fu, W.; Wang, L. Novel Peripherally Restricted Cannabinoid 1 Receptor Selective Antagonist TXX-522 with Prominent Weight-Loss Efficacy in Diet Induced Obese Mice. *Front. Pharmacol.* 2017, 8, 707. [CrossRef]

150. Rover, S.; Andjelkovic, M.; Benardeau, A.; Chaput, E.; Guba, W.; Hebeisen, P.; Mohr, S.; Nettekoven, M.; Obst, U.; Richter, W.F.; et al. 6-Alkoxy-5-aryl-3-pyridinecarboxamides, a new series of bioavailable cannabinoid receptor type 1 (CB1) antagonists including peripherally selective compounds. *J. Med. Chem.* 2013, 56, 9874–9896. [CrossRef]

151. Fulp, A.; Zhang, Y.; Bortoff, K.; Seltzman, H.; Snyder, R.; Wiethe, R.; Amato, G.; Maity, R. Pyrazole antagonists of the CB1 receptor with reduced brain penetration. *Bioorg Med. Chem.* 2016, 24, 1063–1070. [CrossRef]

152. Amato, G.S.; Manke, A.; Vasukuttan, V.; Wiethe, R.W.; Snyder, R.W.; Runyon, S.P.; Maity, R. Synthesis and pharmacological characterization of functionalized 6-piperazin-1-yl-purines as cannabinoid receptor 1 (CB1) inverse agonists. *Bioorg Med. Chem.* 2018, 26, 4518–4531. [CrossRef] [PubMed]
153. Han, J.H.; Shin, H.; Rho, J.G.; Kim, J.E.; Son, D.H.; Yoon, J.; Lee, Y.J.; Park, J.H.; Song, B.J.; Choi, C.S.; et al. Peripheral cannabinoid 1 receptor blockade mitigates adipose tissue inflammation via NLRP3 inflammasome in mouse models of obesity. *Diabetes Obes. Metab.* **2018**, *20*, 2179–2189. [CrossRef]

154. Han, J.H.; Shin, H.; Park, J.Y.; Rho, J.G.; Son, D.H.; Kim, K.W.; Seong, J.K.; Yoon, S.H.; Kim, W. A novel peripheral cannabinoid 1 receptor antagonist, AJ5012, improves metabolic outcomes and suppresses adipose tissue inflammation in obese mice. *FASEB J.* **2019**, *33*, 4314–4326. [CrossRef] [PubMed]

155. Fulp, A.; Bortoff, K.; Seltzman, H.; Zhang, Y.; Mathews, J.; Snyder, R.; Fennell, T.; Maitra, R. Design and synthesis of cannabinoid receptor 1 antagonists for peripheral selectivity. *J. Med. Chem.* **2012**, *55*, 2820–2834. [CrossRef] [PubMed]

156. Hernandez-Vazquez, E.; Ocampo-Montalban, H.; Ceron-Romero, L.; Cruz, M.; Gomez-Zamudio, J.; Hiriart-Valencia, G.; Villalobos-Molina, R.; Flores-Flores, A.; Estrada-Soto, S. Antidiabetic, antidyslipidemic and toxicity profile of ENV-2: A potent pyrazole derivative against diabetes and related diseases. *Eur. J. Pharmacol.* **2017**, *803*, 159–166. [CrossRef]

157. Chen, W.; Liu, H.; Guan, H.; Xue, N.; Wang, L. Cannabinoid CB1 receptor inverse agonist MJ08 stimulates glucose production via hepatic sympathetic innervation in rats. *Eur. J. Pharmacol.* **2017**, *814*, 232–239. [CrossRef] [PubMed]

158. Chen, W.; Xu, C.; Liu, H.Y.; Long, L.; Zhang, W.; Zheng, Z.B.; Xie, Y.D.; Wang, L.L.; Li, S. Novel selective cannabinoid CB(1) receptor antagonist MJ08 with potent in vivo bioactivity and inverse agonistic effects. *Acta Pharmacol. Sin.* **2011**, *32*, 1148–1158. [CrossRef] [PubMed]

159. Seltzman, H.H.; Maitra, R.; Bortoff, K.; Henson, J.; Reggio, P.H.; Wesley, D.; Tam, J. Metabolic Profiling of CB1 Neutral Antagonists. *Methods Enzymol.* **2017**, *593*, 199–215.

160. Hurst, D.; Umejiego, U.; Lynch, D.; Seltzman, H.; Hyatt, S.; Roche, M.; McAllister, S.; Fleischer, D.; Kapur, A.; Abood, M.; et al. Biarylpyrazole inverse agonists at the cannabinoid CB1 receptor: importance of the C-3 carboxamide oxygen/lysine3.28(192) interaction. *J. Med. Chem.* **2006**, *49*, 5969–5987. [CrossRef]