

Review

The Peripheral Cannabinoid Receptor Type 1 (CB₁) as a Molecular Target for Modulating Body Weight in Man

Saoirse Elizabeth O'Sullivan ^{1,*}, Andrew S. Yates ¹ and Richard K. Porter ²¹ Artelo Biosciences, Solana Beach, CA 92075, USA; andy@artelobio.com² School of Biochemistry & Immunology, Trinity Biomedical Sciences Institute (TBSI), Trinity College Dublin, D02R590 Dublin, Ireland; rkporter@tcd.ie

* Correspondence: sosullivan@artelobio.com; Tel.: +1-44-11-5922-5128

Abstract: The cannabinoid 1 (CB₁) receptor regulates appetite and body weight; however, unwanted central side effects of both agonists (in wasting disorders) or antagonists (in obesity and diabetes) have limited their therapeutic utility. At the peripheral level, CB₁ receptor activation impacts the energy balance of mammals in a number of different ways: inhibiting satiety and emesis, increasing food intake, altering adipokine and satiety hormone levels, altering taste sensation, decreasing lipolysis (fat break down), and increasing lipogenesis (fat generation). The CB₁ receptor also plays an important role in the gut–brain axis control of appetite and satiety. The combined effect of peripheral CB₁ activation is to promote appetite, energy storage, and energy preservation (and the opposite is true for CB₁ antagonists). Therefore, the next generation of CB₁ receptor medicines (agonists and antagonists, and indirect modulators of the endocannabinoid system) have been peripherally restricted to mitigate these issues, and some of these are already in clinical stage development. These compounds also have demonstrated potential in other conditions such as alcoholic steatohepatitis and diabetic nephropathy (peripherally restricted CB₁ antagonists) and pain conditions (peripherally restricted CB₁ agonists and FAAH inhibitors). This review will discuss the mechanisms by which peripheral CB₁ receptors regulate body weight, and the therapeutic utility of peripherally restricted drugs in the management of body weight and beyond.

Keywords: CB₁ receptor; peripheral; body weight; appetite; drug discover; cannabinoid



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1. Introduction

A well characterized feature of cannabis use is the stimulation of appetite and suppression of nausea. This effect of cannabis was thought to be primarily mediated by the phytocannabinoid Δ^9 -tetrahydrocannabinol (THC) binding to the CB₁ receptor in key areas of the brain that regulate feeding and nausea including the hypothalamus (feeding), dorsal vagal complex and insular cortex (nausea), and nucleus accumbens and limbic areas (reward and motivation aspects of feeding) [1,2]. For this reason, cannabis has been used to treat the loss of appetite and body weight in several disorders. Synthetic forms of THC (dronabinol and Nabilone[®]) are approved for chemotherapy-induced nausea and vomiting across many countries, supported by meta-analyses of trial data in cancer patients, showing cannabinoids are effective at treating nausea and vomiting [3] and increasing appetite [4]. Dronabinol also causes significant weight gain in patients who are HIV-positive [5,6] (and is approved for HIV/AIDS-induced anorexia in some regions), young anorexic women [7,8], and in patients with Alzheimer's disease [9].

Conversely, antagonising the CB₁ receptor suppresses appetite and causes weight loss, and this has also been exploited therapeutically. The CB₁ receptor blood–brain barrier (BBB) penetrable antagonist (and potentially inverse agonist [10]) Rimonabant (Acomplia[®]) was developed by Sanofi and licensed as an anti-obesity drug. Multiple randomized controlled trials (RCTs) showed that 20 mg rimonabant led to significant reductions in body

weight and haemoglobin A1c (HbA1c), improved lipid profiles, and increased adiponectin (a metabolism-regulating adipokine) [11,12].

However, activation of central CB₁ receptors can be associated with a side effect profile (such as euphoria, dizziness, memory loss, tiredness, and paranoia) that is not always well tolerated by patients, which has limited the use of centrally acting CB₁ agonists in wasting disorders. Additionally, THC targets multiple receptors and ion channels other than cannabinoid receptors, some of which have weight loss promoting effects, such as GPR119 and PPAR α . The currently licensed medicines in this space are dronabinol and Nabilone, both synthetic versions of THC, and their pharmacology may not be selective enough to achieve the desired weight gain in patients.

Antagonising central CB₁ receptors is also associated with CNS-mediated neuropsychiatric side effects such as low mood, reduced joy, anxiety, depression, and suicidal ideology, due to the important role that CB₁ receptors play in the brain's reward system [13]. Indeed, rimonabant was withdrawn from clinical use in 2009 because of significant psychiatric adverse events (AEs) [11,14].

Considering the major contribution of the peripheral CB₁ receptors in body weight control (for reviews see [1,15,16]), an alternative pharmaceutical development pathway is to peripherally restrict CB₁ molecules to get the benefit of modulating peripheral CB₁ receptors without the side effects of modulating central CB₁ receptors. Such a strategy is being pursued by multiple pharmaceutical companies for the development of second- and third-generation anti-obesity CB₁ receptor antagonists (for reviews see [10,17,18]). Peripherally restricted CB₁ agonists are now also being used to gain the benefits of increased feeding and weight gain/maintenance in cancer cachexia.

This review will discuss the mechanisms by which peripheral CB₁ receptors regulate body weight, and the therapeutic utility of peripherally restricted drugs (both agonists, antagonists, and endocannabinoids modulators) in the management of body weight, and in novel therapeutic areas such as chronic kidney disease, pulmonary fibrogenesis, pain, and bladder disorders. The role of CB₁ receptor signaling in the central control of feeding have been reviewed elsewhere [1,19].

2. Peripheral CB₁ Receptors

At the peripheral level, extensive research has shown that CB₁ receptor activation impacts the overall energy balance of mammals in a number of different ways, inhibiting satiety and emesis, increasing food intake, altering adipokine and satiety hormone levels, altering taste sensation, decreasing lipolysis, and increasing lipogenesis. Table 1 summarizes some of the known effects of CB₁ activation in the various organs and body systems that play a role in body weight regulation, illustrated in Figure 1. The combined effect of peripheral CB₁ activation is to promote appetite and promote energy storage and preservation, ultimately leading to weight gain or weight maintenance.

Important locations of peripheral CB₁ receptors include the oral cavity, gastrointestinal tract, afferent vagus nerves, adipose tissue, liver, and pancreas. Mendizabal-Zubiaga and colleagues demonstrated CB₁ to also be associated with mitochondria in skeletal, myocardial, and striated muscle, implicating CB₁ with direct involvement in peripheral energy metabolism [20]. Selective knockdown of CB₁ in adipose tissue [21], the liver [22], or skeletal muscle [23] all prevent diet-induced obesity or hyperphagia. Mice in whom CB₁ was selectively knocked down in the intestinal epithelium did not have the preference for a Western style diet (with reduced caloric intake and meal size) normally observed in wild-type mice [24]. In a preclinical model of cachexia, it was recently shown that the potent, selective CB₁/CB₂ agonist WIN55,212-2 led to a significant reduction in the cachexia index and significantly prevented the cachexia-induced increase in gastric emptying [25].

There is strong correlative evidence from human studies that an active endocannabinoid system (ECS) is associated with visceral and subcutaneous fat accumulation [26], which is supported by many studies that CB₁ activation promotes fat cell differentiation and fat storage (see Table 1 and Figure 1 for details). For instance, in a human study by

Côté and colleagues, plasma 2-arachidonoylglycerol levels correlate positively with body mass index (BMI), waist girth, intra-abdominal adiposity, fasting plasma triglyceride, and insulin levels but negatively with high-density lipoprotein cholesterol and adiponectin [27]. However, visceral fat accumulation is an important correlate with insulin resistance, and higher circulating endocannabinoids have been associated with insulin resistant obese patients [28]. The fact that there are abundant CB₁ receptors in visceral adipose tissue serves as means to target obesity and insulin resistance in human with peripheral CB₁ receptor antagonists or indeed promote weight gain with peripheral CB₁ receptor agonists.

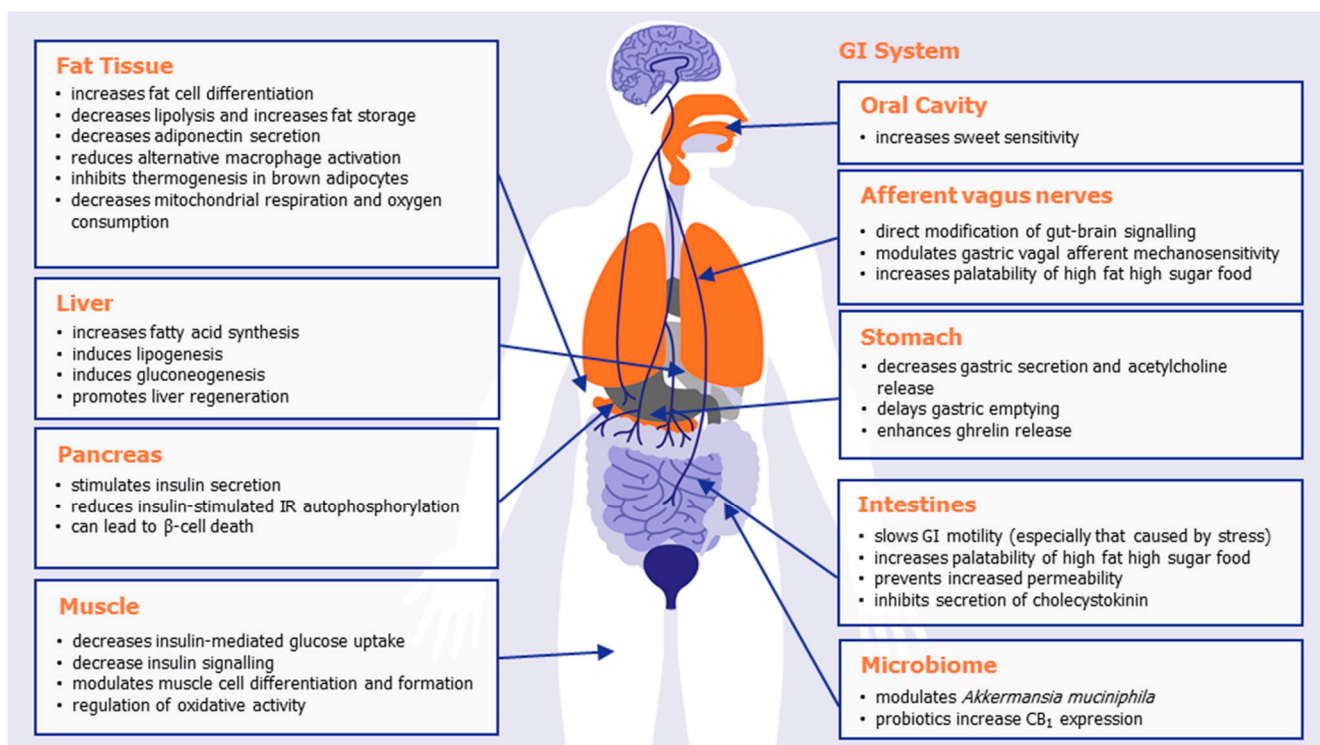


Figure 1. The effects of peripheral CB₁ activation in promoting appetite, food storage, and weight gain.

Activation of hepatic CB₁ has been shown to be associated with obesity and insulin resistance (see Table 1). Measured observations include impaired metabolic function, impaired glucose and lipid metabolism, and augmentation of oxidative stress and inflammatory responses. Blocking peripheral CB₁ in liver not only has weight loss potential, but also the potential to increase insulin sensitivity and glucose metabolism in humans while reducing the potential for hepatic steatosis [29]. It is worth noting that medicines that activate the CB₁ receptor like nabilone may cause mild increase in serum liver enzymes but no cases of clinically apparent liver injury attributable to nabilone [30].

In human skeletal muscle studies, Eckardt and colleagues demonstrated that activation of the CB₁ receptor decreases insulin-mediated glucose uptake and AKT activation in cultured cells [31]. Cavuto and colleagues also demonstrated an attenuating effect of cannabinoid signalling on cultured human muscle cell oxidative pathways in vitro, while CB₁ receptor antagonism increases whole body oxygen consumption [32]. In myotubes cultured from lean individuals, anandamide (AEA) treatment increases expression of pyruvate dehydrogenase kinase 4 (PDK4), an inhibitor of the pyruvate dehydrogenase complex, an enzyme which links glycolysis to the Krebs cycle, while CB₁ antagonism decreases PDK4 expression. PDK4 is a negative regulator of glucose oxidative metabolism in mitochondria, but is an enzyme that is also physiologically inhibited to facilitate fatty acid oxidation. A series of studies from Iannotti and colleagues show an important role of the CB₁ receptor in skeletal muscle cell differentiation and found that CB₁ receptor antagonism (using rimonabant, intra peritoneally) was beneficial at preventing the locomotor deficits

in an animal model of Duchenne muscular dystrophy [33,34]. Genetic inhibition of skeletal muscle receptor was also found to improve mitochondrial performance, whole-body muscle energy expenditure, and physical endurance [23]. These studies indicate an important role for CB₁ in skeletal muscle function and metabolism.

Together, these data demonstrate that there are important direct effects of CB₁ receptor activation in adipose tissue, the GI tract, skeletal muscle, and the liver that drive the effects of CB₁ (agonism or antagonism) on body weight modulation.

Table 1. An overview of some of the effects of CB₁ activation in various organs and body systems that play a role in metabolism. The combined effect of peripheral CB₁ activation is to promote appetite, and energy storage and preservation.

System/Organ	Tissue/Cell	Effect of CB ₁ Activation
GI system	Oral cavity	CB ₁ receptors are expressed in type II taste cells that also express the sweet-taste receptor, and their activation increases sweet sensitivity [35]. CB ₁ receptors on the tongue increase gustatory nerve responses [35].
	Stomach	CB ₁ is expressed on acid-secreting parietal cells [36]. CB ₁ activation decreases gastric secretion and acetylcholine release [37]. CB ₁ activation delays gastric emptying [38]. CB ₁ is expressed in ghrelin-positive gastric mucosal cells [39]. CB ₁ activation enhances ghrelin release from the stomach [40].
	I cells of the small intestine	CB ₁ is expressed in enteroendocrine cells [41]. CB ₁ inhibits the secretion of the satiation hormone cholecystokinin [41].
	Intestines	CB ₁ activation slows GI motility, particularly stress-induced motility [42,43]. CB ₁ activation prevents increased intestine permeability (leaky guts) [44]. Intestinal CB ₁ activation important for palatability of high fat high sugar foods [45]. CB ₁ deletion in intestinal epithelium reduces western diet preferences [24].
	Afferent vagus nerves	CB ₁ receptors are expressed on vagal terminals [46,47]. Fasting increases CB ₁ expression on vagal afferent neurons [47]. The induction of feeding by peripherally CB ₁ activation is inhibited by vagal ablation [48]. CB ₁ activation modulates gastric vagal afferent mechanosensitivity to stretch/distension (leading to feeling of fullness) [39].
	Microbiome	CB ₁ receptor antagonism [49] or THC [50] increases <i>Akkermansia muciniphila</i> . Probiotic treatment increases CB ₁ and/or CB ₂ expression [51,52].
	Fat tissue	Adipocytes
White adipocyte mitochondria		CB ₁ activation decreases mitochondrial respiration and oxygen consumption [57,58].
Brown adipose tissue (BAT)		CB ₁ is upregulated during activation of BAT [59,60]. CB ₁ antagonism increases expression of uncoupling protein 1 (UCP-1) [61].
Liver	Hepatocytes	CB ₁ activation increases lipogenesis [62]. CB ₁ activation increases fatty acid synthesis [62]. CB ₁ activation induces gluconeogenesis [63]. CB ₁ activation promotes liver regeneration by increasing mitotic progression [64]. CB ₁ knock-out mice are protected against diet-induced lipogenesis and steatosis [65].
Pancreas	Pancreatic β -cells	CB ₁ activation stimulates basal and glucose-dependent insulin secretion [66,67]. CB ₁ activation impedes insulin-stimulated IR autophosphorylation [68]. CB ₁ receptors can lead to β -cell death [69].
Muscle	Skeletal muscle cells	CB ₁ expression increases during skeletal muscle cell differentiation [31,33]. CB ₁ activation decreases insulin-mediated glucose uptake [31]. CB ₁ knockdown improves mitochondrial performance, increases whole-body muscle energy expenditure, and improves physical endurance [23]. CB ₁ receptor knockdown prevents diet-induced and age-induced insulin resistance [23].

Table 1. Cont.

System/Organ	Tissue/Cell	Effect of CB ₁ Activation
Muscle	Myotubules	CB ₁ activation prevents myotubule formation [33]. CB ₁ activation inhibits sarcoplasmic Ca ²⁺ release [70].
	Skeletal muscle satellite cells	CB ₁ activation inhibits satellite cell differentiation [34].
	Muscle Mitochondria	CB ₁ receptors regulates mitochondrial oxidative activity [20].

2.1. Effects of Peripheral CB₁ Receptors on Appetite Hormones

In addition to the direct effects of CB₁ activation in peripheral tissues, there are humoral and neuronal links between peripheral CB₁ receptors and the central pathways controlling body weight through the modulation of key hormones that influence appetite.

Leptin is an adipose-derived hormone that acts on central receptors to reduce feeding and appetite, and leptin resistance is a feature of obesity. Cross-talk between central leptin and CB₁ receptors has been well documented, but leptin resistance in diet-induced obese mice can be reversed by the peripherally restricted CB₁ antagonist JD5037 [71], demonstrating that CB₁ receptors also modulate leptin sensitivity at a peripheral level, and this plays an important role in the ability of peripheral CB₁ blockade to mediate hypophagia and weight loss.

Ghrelin is a peptide hormone released in the gastrointestinal tract (mainly in the stomach and pancreas) and the brain that acts on receptors located on the vagus to stimulate appetite. The CB₁ receptor is expressed in the neuroendocrine cells of the stomach that secrete ghrelin, and CB₁ antagonism reduces ghrelin secretion, preventing appetite stimulation [40]. The peripheral-restricted CB₁ antagonist LH-21 was also found to block ghrelin-induced hyperphagia in free feeding animals [72]. Thus, the anorexigenic effect of CB₁ antagonists is at least partially a consequence of decreased gastric ghrelin secretion, and conversely CB₁ activation in the stomach will increase ghrelin, stimulating appetite and food intake through ghrelin's actions on the vagal nerve. This is supported by recent human studies that showed increased plasma levels of ghrelin after oral THC [73,74]. The ghrelin agonist anamorelin (Adlumiz[®]) has been approved in Japan for the treatment of cancer cachexia, demonstrating the utility of increasing ghrelin to improve anorexic and cachexic conditions [75].

Cholecystokinin (CCK) is a peptide hormone release from the duodenum during digestion, which acts as a hunger suppressant at receptors located on the vagus (mainly) and in the brain. The CB₁ receptor is expressed on endocrine cells of the intestinal epithelium that secrete CCK, and activation of CB₁ blocks the secretion of CCK (and the opposite true of CB₁ antagonists) [41]. The same study showed that the hypophagic effect of a peripherally restricted CB₁ antagonist in obese mice was reversed by co-administration with a CCK receptor antagonist, indicating the importance of CB₁ regulation over this appetite suppressant hormone.

Together, these studies show that peripheral activation of CB₁ modulates the activity of the key appetite-regulating hormones leptin, ghrelin, and CCK, whose receptors are located in the brain, or on the vagus nerve with direct influence on the brain via the gut–brain axis.

2.2. Gut–Brain Axis

In addition to the hormonal influence on the central integration of appetite, CB₁ receptors are expressed on vagal terminals throughout the GI tract, playing a direct role in the modulation of afferent information to the brain and the regulation of food intake (see [76] for an extensive review on this topic). GI vagal afferents play an important role in the peripheral regulation of food intake via signalling the degree of distension of the stomach, which leads to feelings of fullness and satiety. CB₁ activation inhibits the vagal afferent

response to tension, thus preventing the feeling of fullness and allowing food consumption to continue [39,77].

Levels of the endogenous CB₁ agonists anandamide and 2-AG increase in the intestine in the starved state or by (lipid) feeding, and this stimulates feeding, which is abolished after sensory deafferentation or CB₁ receptor antagonism [48,78]. Argueta and DiPatrizio showed that the hyperphagia in mice given free access to a high-fat and sucrose diet was inhibited by a peripherally restricted CB₁ antagonist [45]. These researchers went on to show that mice in whom CB₁ was selectively knocked down in the intestinal epithelium did not have the preference for the high-fat and sucrose diet [24]. Thus, endogenous activation of CB₁ in the intestine increases the palatability of food through gut–brain communication.

2.3. Microbiome

A novel mechanism of action for CB₁ in the modulation of metabolism and body weight may be through modifications in the microbiome (see [79] for a recent review). Mehrpouya-Bahrami and colleagues found that a CB₁ antagonist caused changes in the gut microbial community with an increase in Akkermansia muciniphila (Verrucomicrobiaceae family) and a decrease in the Lachnospiraceae and Erysipelotrichaceae families, although it is not clear if this was a direct effect or secondary to the improvements in metabolic dysfunction [49]. Chronic THC treatment prevented the diet-induced obesity changes in gut microbiota, particularly causing an increase in Akkermansia muciniphila [50]. Probiotic treatment has also been shown to increase CB₁ and CB₂ expression in colonic mucosa and adipose tissue [52], which was associated with improvements in disease activity in dogs with gut dysmotility disturbances [51]. Conversely, studies using germ-free mice have shown that there is an upregulation of CB₁ in the intestines that is reversed after faecal microbiota transfer [80]. These emerging studies suggest a link between the endocannabinoid system and gut bacteria that may play a role in the modulation of body weight by CB₁ at the peripheral level.

3. Therapeutic Utility of Peripheral CB₁ Receptors as Molecular Targets

3.1. Peripherally Restricted CB₁ Antagonists

After the withdrawal of Rimonabant, researchers began developing peripherally restricted CB₁ antagonists in obesity and diabetes. Molecules such as URB447 (a mixed CB₁/CB₂ neutral antagonist) [81], AM6545 (a CB₁ neutral antagonist) [82], TXX-522 (a CB₁ selective antagonist) [83], and LH-21 (a CB₁ neutral antagonist) [72,84] were shown to reduce feeding and body weight gain in rodents. In models of diabetes, peripherally restricted CB₁ antagonists improve glucose tolerance and insulin sensitivity [85]. This class of drugs also ameliorate other conditions associated with obesity and diabetes such as leptin resistance, fatty liver, and dyslipidemia [86,87] and reverse hyperphagia, body weight, and metabolic syndrome in a genetic model of Prader–Willi syndrome [88].

Another strategy to avoid the side effects of CB₁ antagonists is through allosteric modulation of the CB₁ receptor. The negative allosteric modulators ORG27569 [89], RVD-hemopressin(α) [90], and PSNCBAM-1 [91] reduce food intake with or without a reduction in body weight in rats.

In addition to metabolic disorders, preclinical research suggests peripherally restricted antagonists have beneficial effects on kidney diseases [92,93], liver fibrosis and steatosis [94–96], pulmonary fibrosis [97,98], and alcoholism [99] (see Table 2). In some cases, some third-generation compounds have been designed to inhibit more than one molecular target. For example, hybrid inhibitors of the CB₁ receptor and inducible nitric oxide synthase (iNOS) show benefits in alcohol-drinking behaviors [100], kidney diseases [101], liver fibrosis [102], and skin fibrosis [103].

Several pharmaceutical companies are developing medicines to inhibit the peripheral CB₁ receptor (see Table 2).

Inversago Pharma has been granted rare paediatric disease designation by Food and Drug Administration (FDA) for the treatment of Prader–Willi syndrome with their periph-

erally restricted CB₁ inverse agonist INV-101. The safety, tolerability, and pharmacokinetics of single ascending oral doses of INV-101 is being tested in healthy volunteers, although this trial is not recruiting at the time of writing (ClinicalTrials.gov Identifier: NCT04531150).

GFB-024 is a peripherally restricted CB₁ inverse agonist monoclonal antibody intended to treat patients with severe insulin-resistant diabetic nephropathy (DN) in development by Goldfinch Bio (<https://www.goldfinchbio.com/pipeline/gfb-024/> (accessed on 10 September 2021)). Goldfinch Bio have just announced a phase 1 clinical trial to evaluate the safety and pharmacokinetics of single and repeated dosing of GFB-024 in overweight healthy volunteers (ClinicalTrials.gov Identifier: NCT04880291).

A phase 1 trial with the peripherally selective neutral CB₁ antagonist TM38837 from 7TM Pharma has been conducted in healthy subjects [104], although it is unclear whether this is an active drug development program.

JD5037 is a peripherally restricted CB₁ inverse agonist developed by Jenrin Discovery and licensed to Corbus Pharmaceuticals (now CRB-4001), which is due to begin phase 1 testing in the first half of 2022 (<https://www.corbuspharma.com/our-pipeline/endocannabinoid-system> (accessed on 10 September 2021)).

Table 2. Potential therapeutic utility of peripherally restricted compounds targeting the CB₁ receptor directly or indirectly.

	Peripherally Restricted CB ₁ Antagonists	Peripherally Restricted CB ₁ Agonists	Peripherally Restricted FAAH Inhibitors
Preclinical research	Obesity [81–83,86] Type 2 diabetes [85,105] Prader–Willi syndrome [88] Chronic kidney disease [101] Diabetic nephropathy [93] Alcoholic liver steatosis [94] Alcoholism [99,100] Non-alcoholic liver steatosis [96] Obesity-related liver steatosis [95] Liver fibrosis [102] Pulmonary fibrogenesis [97,98] Skin fibrosis [103]	Inflammatory pain [106,107] Neuropathic pain [107,108] Bone cancer pain [109] Chemotherapy-induced pain [110] Migraine and medication overuse headache [111] Spasticity in multiple sclerosis [112] Gastrointestinal motility in colitis [42,43] Anticipatory nausea [113] Cardiac disease [114]	Neuropathic pain [115] Chemotherapy-induced neuropathy [116] Inflammatory pain [115,117,118] Diabetic neuropathy [119] Visceral pain [115] Migraine [120,121] Anticipatory nausea [113] Cystitis [122] Bladder overactivity [123] Gastric lesions [118]
Clinical research	INV-101 in Prader–Willi syndrome (PWS) and non-alcoholic steatohepatitis (NCT04531150) (Inversago Pharma) TM38837 in healthy subjects [104] (7TM Pharma) GFB-024 in diabetic nephropathy (Goldfinch Bio, NCT04880291)	AZD1940 in capsaicin-induced pain [124] and post-operative pain [125] ART27.13 (previously AZD1940) in Cancer anorexia (EudraCT NUMBER:2020-000464-27) (Artelo Biosciences)	URB937 is in the early stages of clinical development (Exxel Pharma)

3.2. Peripherally Restricted CB₁ Agonists

After the discovery of the CB₁ receptors and their important role in pain modulation, the first significant drug discovery program for peripherally restricted CB₁ agonists was analgesics. The concept was to utilize the analgesic effects of CB₁ activation without the CNS side effects, and extensive preclinical studies have demonstrated the analgesic effects of these compounds across various models of pain [126]. However, a lack of efficacy in clinical studies [124,125] meant the pharmaceutical development of these medicines was terminated. However, preclinical research with peripherally restricted CB₁ agonists continues in cancer-related pain [109,110] and migraine [111]. Other indications that have been investigated with a peripherally restricted CB₁ agonist included spasticity in multiple sclerosis [112], gastrointestinal motility issues [42,43], and anticipatory nausea [113], although none of these have been taken to clinic (see Table 2).

By contrast to the large number of peripherally restricted CB₁ antagonists in development for obesity and related metabolic disorders, far less work has been carried out to potential exploit CB₁ activation in the periphery to promote weight gain. Although appetite stimulants such as the progesterone megestrol acetate, and the steroid dexamethasone, have been used for treatment of anorexia associated with cancer, no drugs have been approved for this indication in the United States or Europe, with the exception of dronabinol, which is approved for HIV/AIDS-induced anorexia only. Thus, the development of novel pharmaceutical strategies to stimulate appetite in chronic states of anorexia (such as cancer, chronic kidney disease, and heart failure) is still a significant unmet need. ART27.13 is a CB₁/CB₂ receptor agonist with reduced brain penetration originally developed by AstraZeneca for analgesia, now being developed by Artelo Biosciences. In a multiple-dose ascending study, a dose-dependent increase in body weight was observed (see Figure 2, ClinicalTrials.gov Identifier: NCT00689780, data on file) that was not explained by fluid retention; it was likely due to increased appetite and food intake. The clinical potential of ART27.13 to increase appetite leading to weight gain in patients with cancer anorexia is being trialed in a Phase 1b/2a study (EudraCT NUMBER:2020-000464-27).

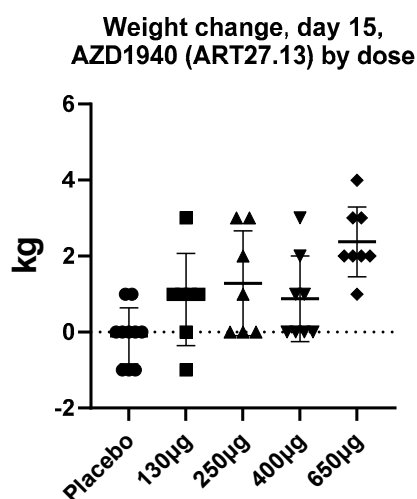


Figure 2. The mean increase in body weight (kg) after 15 days daily treatment with AZD1940 (ART27.13) in healthy volunteers in a dose-ascending study (ClinicalTrials.gov Identifier: NCT00689780, data on file). Data are presented as a scatterplot with mean and SD.

3.3. Peripherally Restricted Fatty Acid Amide Hydrolase (FAAH) Inhibitors

Indirect activation of peripheral cannabinoid receptors can also be achieved through peripherally restricted fatty acid amide hydrolase (FAAH) inhibitors, which increase endocannabinoid tone and promote activation of cannabinoid receptors. Such compounds have been shown in preclinical research models to be analgesic in many models, including neuropathic pain [115], diabetic neuropathy [119], chemotherapy (paclitaxel)-induced pain [116], inflammatory pain [115,117,119], visceral pain [115], and migraine and medication overuse headache [120,121] (see Table 2). Peripherally restricted FAAH inhibitors also reduce anticipatory nausea [113], protect against non-steroidal anti-inflammatory agent-induced gastric lesions [118], and reduce hyperactivity in the rat bladder induced by PGE prostaglandin E₂ [123] and in an LPS model of cystitis [122].

The peripherally restricted FAAH inhibitor URB937 is in development by ExxelPharma for chronic neuropathic pain; although human clinical studies have not yet begun (<https://exxelpharma.com/pipeline/overview/> (accessed on 10 September 2021)), the use of this alternative strategy to activate peripheral cannabinoid receptors looks promising.

4. Conclusions

Drug discovery efforts to develop CB₁ agonists and antagonists were hampered by CNS-mediated side effects of these drugs. Second- and third-generation compounds in

this area have tried to circumvent these adverse effects by selectively activating the CB₁ receptor expressed in the peripheral nervous system and major organ systems of the body. Preclinical investigation supports the importance of the CB₁ receptor throughout the gastrointestinal tract, adipose tissue, liver, pancreas, and skeletal muscle, as well as mediating humoral and afferent satiety signals to the brain. Preclinical efficacy data support the therapeutic utility of peripherally restricted CB₁ agonists in pain management, and antagonists in obesity, metabolic syndrome, and liver diseases. Preclinical data also support indirect activation of peripheral CB₁ receptors through peripherally-restricted FAAH inhibitors in pain management and bladder conditions. Translation of these findings into the clinical arena is emerging, with several pharmaceutical companies developing novel medicines in early phase 1 and 2 trials in weight gain in cancer anorexia (agonist: ART27.13), and in metabolic conditions (antagonists: INV-101, TM38837, and GFB-024), which, if successful, could result in novel, rationally designed synthetic cannabinoid medicines that demonstrate the appropriate benefit–risk profile to allow mainstream use in the modulation of weight by targeting CB₁.

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