J. Pharm. Res. 2026;25(2):98-105

Print ISSN: 0973-7200
Online ISSN: 2454-8405

Journal of Pharmaceutical Research

REVIEW ARTICLE

Peripherally Selective CB1 Receptor Antagonists: A Promising Therapeutic Strategy for Metabolic Disorders

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ARTICLE INFO

Article history:
Received 24-04-2026
Accepted 26-05-2026
Published 03-06-2026

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https://doi.org/10.18579/jopcr/v25.i2.98

ABSTRACT

Metabolic disorders, such as obesity, type 2 diabetes mellitus, dyslipidemia and hypertension, are one of the fastest-growing health issues across the world due to insulin resistance, low-grade chronic inflammation, and disrupted energy homeostasis. The endocannabinoid system (ECS) is a crucial factor in the regulation of appetite, glucose and lipid metabolism, inflammatory signalling, and energy balance, as the cannabinoid type 1. CB1 receptor has become a major molecular mediator in the pathogenesis of metabolic diseases. Initial clinical trials showed that pharmacological inhibition of the CB1 receptor could promote body weight, glycemic and lipid profile and cardiometabolic risk factors; first-generation centrally acting CB1 antagonists, like rimonabant, were discontinued because of unacceptable neuropsychiatric adverse effects. This constraint led to a paradigm shift in the creation of the peripherally restricted CB1 receptor antagonist that maintains metabolism efficacy and limits exposure to the central nervous system (CNS). The role of the peripheral CB1 receptor in obesity, insulin resistance, dyslipidemia, and hypertension is critically discussed in this review, and the mechanisms by which CB1 blockade improves insulin sensitivity, reduces lipid accumulation, attenuates inflammation, and maintains glucose homeostasis are elucidated. The emerging technology in medicinal chemistry has resulted in the discovery of novel peripherally selective CB1 antagonists, such as RTI1092769, INV-202, BAR-1, otenabant and thioamide-based antagonists, which exhibit encouraging preclinical efficacies with reduced safety profiles. Moreover, contemporary obstacles in clinical translation, regulatory mechanisms, and prospects of using combination therapy, precision medicine, and targeting with tissue are also described. Taken together, the peripherally selective CB1 receptor blockade is a mechanistically well-founded and highly promising therapeutic approach in the treatment of metabolic disorders.

Keywords: Cannabinoid type-1 receptor, Endocannabinoid system, Metabolic disorder, Type 2 diabetes mellitus, Obesity

INTRODUCTION

The Cannabinoid-1 receptor antagonists are developed for treating weight issues and diabetes, focusing on using the Cannabinoid system for metabolic purposes in developing a restricted peripheral antagonist that does not cause any of the previous drugs' psychiatric symptoms[1]. It focuses on the global health crisis of obesity and diabetes, but the system is based on energy balance and the evolution of CB1 receptor antagonists, from initial failure to current promising strategies.

THC, also known as delta-9-tetrahydrocannabinol (THC), is the main psychoactive compound found in marijuana. The discovery of THC occurred approximately 50 years ago, as did the identification of the Endocannabinoid system (ECS). The ECS is an endogenous signaling mechanism comprised of specific receptors (CB1 and CB2), endogenous ligands (endocannabinoids), and the enzymes involved in their creation and breakdown[2]. Cannabinoid 1 receptors (CB1) are found throughout the body, including in the brain, CNS, liver, skeletal muscle, pancreas, and adipose tissue (fat)[3].

Metabolic disorders are complex conditions caused by the combined effects of multiple underlying factors, such as obesity, insulin resistance, and persistent low-grade inflammation. The endocannabinoid system strongly influences insulin sensitivity, lipid metabolism, energy balance, appetite regulation, and cellular activity[4].

Obesity

Nowadays, around 1.1 billion individuals globally suffer from obesity, making it an unquestionably global issue[5].

Role of Obesity

The endocannabinoid system (ECS) is a biological mechanism linked to several homeostatic processes in the body, including appetite regulation. The ECS consists of two primary endogenous lipid-soluble ligands (2-arachidonoylglycerol [2-AG] and anandamide [AEA]) and all of the enzymes involved in their synthesis and metabolism[3].

Diabetes

Type -2 diabetes elevated the risk of severe cardiovascular disease since it is intimately linked to abdominal obesity and is typically linked to other cardiometabolic risk factors. Abdominal obesity and diabetes may cause the endocannabinoid system to become overactive, according to several human and animal investigations. Through the activation of the CB1 receptor, both central and systemic endocannabinoid effects encourage adiposity and related metabolism-related alterations. In both non-diabetic and diabetic overweight obese patients, rimonabant, the first selective CB1 receptor blocker in clinical use, has been demonstrated to lower body weight, waist circumference, triglycerides, blood pressure, insulin resistance index, and C-reactive protein levels while raising high-density lipoprotein (HDL) cholesterol and adiponectin concentrations. Additionally, patients with type-2 diabetes who were treated with metformin or sulphonyl urea, as well as those who had never taken medication before, showed a 0.5–0.7% decrease in HbA1c level. Weight loss was unable to account for nearly half of the metabolic alteration, including the decrease in HbA1c, indicating a direct peripheral effect[6]. Studies conducted over the past 20 years have demonstrated the critical role of the ECS in the development of obesity, and its detrimental effect on both glucose and lipid metabolism that can contribute to the development of insulin resistance and type 2 diabetes. Insulin resistance in peripheral tissue and relative deficiency in insulin secretion by the islets of beta cells are both important factors in the development of type 2 diabetes mellitus[7].

Role of Diabetes

- Impaired Insulin sensitivity is the primary cause of type 2 diabetes mellitus, which is linked to gene mutations, genetics, obesity and other factors.
- The rising incidence of these illnesses emphasises how critical it is to understand the underlying biological pathway to support therapeutic intervention[8].
- Recent research showed that CB1 Receptor deletion in beta cells greatly reduced diet-induced intra-islet inflammation and boosted cell proliferation and early-phase insulin secretion[9].

Pathogenesis of Metabolic Syndrome

These days, it's critical to comprehend the pathophysiology of metabolic disorders in order to determine how Cannabinoid 1 receptor blockers may function. However, research will mostly focus on the underlying mechanisms of obesity, dyslipidaemia, insulin resistance, and Hypertension.

Insulin resistance

Insulin resistance is the most favoured theory to explain the pathophysiology of the metabolic syndrome. Thus, the insulin resistance syndrome is also known as metabolic syndrome. This metabolic dysfunction leads to hyperinsulinemia due to inadequate insulin action (in order to maintain euglycemia) and connects multiple seemingly unrelated biological processes into a pathophysiological framework. An excess of circulating fatty acids, which are released from an increased quantity of adipose tissue, is a significant factor in the development of insulin resistance. By preventing insulin- mediated glucose absorption, Free fatty acids lower muscle insulin sensitivity. Hyperinsulinemia is the outcome of increased pancreatic

insulin production brought by elevated blood glucose levels[10].

Dyslipidemia

Central obesity, insulin resistance and hypertension are all part of dyslipidemia, a major component of metabolic syndrome that increases the risk of cardiovascular conditions. Reduced HDL cholesterol and increased triglycerides, apolipoprotein B, free fatty acids, and very low density lipoprotein (VLDL) are its hallmarks. Atherogenic dyslipidemia, which is characterised by the buildup of VLDL, tiny dense LDL, and low HDL–C occurs by the disruption and speeds up the development of atherosclerosis. These lipid abnormalities are made worse by the chronic inflammation seen in metabolic syndrome, which further encourages endothelial dysfunction and plaque development. When combined, inflammatory and metabolic disorders significantly increase the risk of coronary artery disease and other cardiovascular events in people with metabolic syndrome. To reduce long-term cardiovascular risk, the complexity of dyslipidemia in metabolic syndrome requires a customised treatment plan that targets lipid abnormalities and other syndrome components[11].

Hypertension

In both industrialised and developing nations, hypertension is the leading cause of death. One- fourth of people worldwide suffer from hypertension, which is the primary cause of multiple sclerosis. It raises the risk of cardiac issues and renal failure. The primary psychoactive component of marijuana, tetrahydrocannabinol (THC), has been shown to lower blood pressure and heart rate in rodent studies, while chronic use of marijuana has been linked to hypotension in humans. Endogenous cannabinoid ligands, such as arachidonoyl ethanolamine (anandamide) and 2 - arachidonoylglyerol (2-AG), have also been shown to lower blood pressure and heart rate. However, an enhanced hypotensive effect of cannabis has been observed in spontaneously hypertensive rats (SHR)[12].

Obesity

Obesity can be caused by a large disruption of the endocannabinoid system. The endocannabinoid system is responsible for regulating hunger, metabolism (energy), and body weight. An important component of the endocannabinoid system is the receptor that is capable of creating an improved energy balance (leading to weight gain) and increased appetite (leading to decreased energy)[13]. These days, the emphasis has shifted to peripherally restricted CB1 receptor antagonists as an effort to reduce the negative effects of central CB1 receptor blockers. These peripherally acting medications will enhance metabolic health, such as glucose regulation and insulin sensitivity, without entering the central nervous system and producing psychological side effects[14].

HISTORICAL PERSPECTIVE

First generation CB1 Receptor Antagonist

Cannabinoid receptor 1 antagonist may be used to treat multiple disorders, including metabolic disorders. Although the CB1 receptor is distributed throughout the body, they are present in significantly higher concentrations in the central nervous system (CNS)[15]. The first clinically authorised CB1 inverse agonist, Rimonabant, has negative side effects relating to the central nervous system (CNS), which recently stopped the development of other CB1 antagonists. It is useful for improving several metabolic parameters and causing weight loss[16].

Investigations in the last decade have indicated that selective peripheral (liver, skeletal muscle, adipose tissue and pancreas) CB1 antagonism decreases lipogenesis, increases energy expenditure in liver and adipose tissue, and decreases appetite, suggesting that CB1 antagonists that selectively block CB1 receptors in peripheral tissues could be promising new therapeutic approaches for the treatment of metabolic disorders without affecting the central nervous system (CNS) side effects[17]. None of these peripherally restricted CB1 antagonists has been thoroughly studied or demonstrated to be effective in a clinical setting. However, the challenges associated with rimonabant prompted researchers to investigate alternative strategies, such as peripherally restricted CB1 receptor antagonists, which are designed to limit central nervous system penetration and minimise neuropsychiatric adverse effects[15].

Impact of withdrawn medications

The rimonabant withdrawal is an example of the problems encountered with expedited drug approval. Furthermore, the loss of rimonabant (a cannabinoid CB1 receptor antagonist) has had a major impact on the development of new CB1 receptor antagonists for metabolic disorders, including diabetes. Anxiety and depression are two common psychiatric side effects associated with rimonabant[18]. Research on centrally acting CB1 receptor blockers was subsequently discontinued, leading to a shift in focus toward peripherally restricted antagonists that limit penetration into the central nervous system[17].

Disagreement exists concerning the role of the endocannabinoid system in the islet, but some studies have suggested that the activation of CB1 increases insulin release. Most of the research has focused on the peripheral effects of the CB1 receptor, specifically its isoform located in the liver (hepatocytes) and pancreas (β-cells); however, its effects directly on glucose metabolism cannot be excluded at this time[19]. The change in the strategy that resulted in the

creation of a novel CB1 receptor antagonist, with the primary goal of providing therapeutic benefits in treating diabetes and its challenge in avoiding the previously mentioned psychiatric side effects. To ensure patient safety, research has continued to focus on tissue-specific and peripherally restricted approaches that maximise metabolic outcomes[14]. These advancements offer a novel approach to diabetes treatment by harnessing the therapeutic potential of the endocannabinoid system.

CB1 Receptor Blockade: Effects on Weight, Insulin Sensitivity, and Lipid Metabolism

Weight loss[20, 21]:

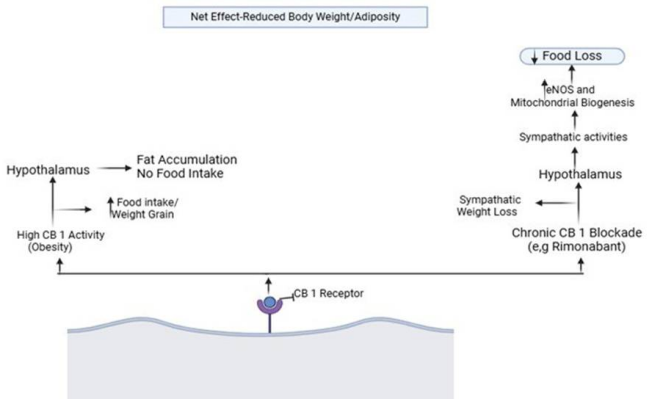

Fig. 1: Weight Loss improved by CB1 receptor Blockade

Insulin Sensitivity[22, 23]:

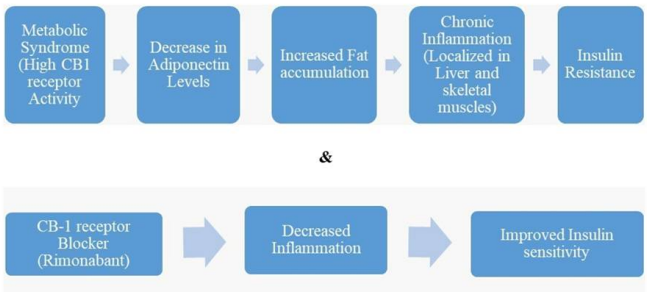

Fig. 2: Insulin sensitivity improved by CB1 receptor blockade

Lipid Metabolism[22]:

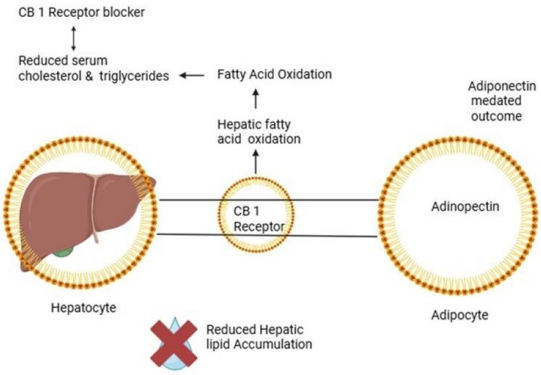

Fig. 3: Lipid metabolism is improved by CB1 receptor blockade

Novel and Peripherally Selective CB1 Blockers

New-Generation CB1 Antagonists Designed to Minimise Central Nervous System Exposure

New generation Cannabinoid receptor 1 (CB1) blockers (antagonist) have been created to minimise exposure to the CNS, especially targeting metabolic disorders like diabetes. Recent developments since 2020 highlight efforts to develop peripherally selective CB1 antagonists that minimize central nervous system–related adverse effects previously observed with compounds such as rimonabant. However, these antagonists, such as RTI1092769 otenabant, BAR-1, INV-202 and thiomide derivatives concentrate on enhancing metabolic parameters without the central adverse effects of previous treatment, such as rimonabant. One peripherally selective CB1 antagonist that shows low brain exposure and improves its safety for the treatment of metabolic disorders is RTI1092769. It focuses on peripheral metabolic modulation and lessens central side effects by targeting the CB 1 receptor outside of the central nervous system. This substance effectively prevented weight gain and enhanced glucose metabolism, making it a promising option for the management of Diabetes[15, 24]. The next generation of CB1 receptor antagonists, such as INV-202 and BAR-1, has demonstrated that endocannabinoids modulate insulin sensitivity at both central and peripheral sites of action. Their peripheral-focused effects have shown improved metabolic outcomes and weight reduction under experimental conditions[25].

This research focuses on peripherally restricted CB1 receptor antagonists to improve metabolic function, manage conditions such as diabetes, and reduce adverse effects associated with the central nervous system. These developments highlight the potential of cannabinoid receptor modulation as an effective therapeutic approach for metabolic disorders.

Efficacy of CB1 Antagonists in Weight and Metabolic Control

A novel cannabinoid CB1 receptor blocker has demonstrated efficacy in controlling metabolism in part because it can reduce weight and improve metabolic parameters. Many other mechanisms target the central and peripheral components of metabolism. Rimonabant (first-generation CB1 receptor blocker) has been shown to have significant effects on body weight reduction and enhancing metabolism parameters in preclinical and clinical studies, including improvements in lipid profile and diabetes management, due to both decreases in food intake and increases in energy expenditure[16]. Peripherally restricted CB1 receptor blockers, whose primary goal is to modify metabolic pathways without impacting the CNS, have become the focus of the side effects study. There is a large amount of evidence that shows in peripheral tissues, including liver, skeletal muscle, adipose tissue and pancreas, blocking the activity of the CB1 receptor is enough to decrease the amount of fat made in the liver and in adipose tissue, increase the energy used by the body for activities, and stop eating food from an external source. For instance, the CB1 receptor in hepatocytes and β–cells is implicated in the metabolic process and is essential for insulin secretion, glucose regulation and targeting receptors that improve metabolic outcome without central adverse effect[21].

Peripheral acting CB1 antagonists are beneficial in promoting weight loss and enhancing metabolic health in a mice model, but they don't cause behavioural side effects that are indicative of neuropsychiatric problems in humans[29].

Pharmacological feature leading to peripheral selectivity

The pharmacological properties that result in peripheral selectivity of novel CB1 receptor blockers in the treatment of metabolic disorders are mostly attributed to the reduction of brain penetration to prevent CNS side effects without compromising the ability to induce action of peripheral tissues that are involved in metabolism. The first generation CB1 blockers, including rimonabant, had a global effect by action on both central and peripheral CB1 receptors but were discontinued because of serious neuropsychiatric adverse events. However, this led to second- and third-generation CB1 antagonists that are peripherally focused and target only CB1 receptors extracerebral, with minimal penetration of the blood-brain barrier.

But the following parameters are-

Limited blood-brain barrier Permeability

Novel CB1 receptor blockers are chemically designed to limit their ability to cross the blood–brain barrier. It is done by enhanced polarity, molecular size and substrate selectivity of efflux transporter, this limiting central CB1 receptor occupancy and avoiding CNS mediated side effects such as anxiety, etc.[17, 26].

Targeting of Peripheral CB1 Isoforms

Certain CB1 receptor isoforms and variants expressed in non-CNS tissues, such as the liver, adipocytes, and insulin-producing pancreatic cells, exhibit variations in their binding profiles. The selectivity and therapeutic advantages of designing ligands that have higher affinity to these peripheral isoforms without central activities are increased in energy metabolism and glucose homeostasis[21].

The Tissue Specific Pharmacodynamics

Moderately selective to peripheral CB1 receptors located in critical metabolic organs (e.g., liver, adipose tissue, pancreas, kidneys) can help regulate insulin sensitivity as well as improve lipid metabolism and adipose tissue-associated inflammation. By blocking the hyperactivity of peripheral CB1 receptors, these agents may also improve metabolic parameters, without having an impact on appetite regulation via the CNS[27-29].

Classification of Receptor Ligands

The designation of some peripherally selective blockers or inverse agonists targeting the peripheral CB1 receptor may be the difference between success and failure because it can control receptor signalling activation without causing complete blockage[30].

Exploiting the Role of the Peripheral Endocannabinoid System

The endocannabinoid system (ECS) peripherally controls energy balance, feeding and metabolic homeostasis. Blockers that are restricted to the peripheral endocannabinoid system avoid central nervous system–related adverse effects while maintaining favourable metabolic outcomes[14, 29]. Finally, novel peripherally selective CB1 blockers have been designed with pharmacokinetic properties that restrict CNS penetration, reliant on peripheral CB1 receptor isoforms and tissue selectivity, and selective pharmacodynamics in order to achieve maximal metabolic property being minimally central side effects.

FUTURE PERSPECTIVES

Potential for combination therapies, precision medicine, and overcoming resistance

In the management of metabolic disorders, especially obesity and related disorders, novel CB1 receptor blockers offer a bright future. Combination medicine, precision medicine and overcoming resistance are important areas of

interest, and these areas will be the focus of future development.

Combination Therapies

Study indicates that co-administration of CB1 receptor antagonists with other medications may enhance therapeutic efficacy. Bifunctional Cannabinoid Ligands, which are both Transient Receptor Potential Vanilloid (TRPV-1) antagonists and CB2 agonists, may have the potential to improve therapeutic success and reduce adverse events[31]. Furthermore, peripherally confined Cannabinoid, which decreases psychoactive effect, can be linked with other metabolic therapies to target specific metabolic routes without affecting the CNS[29].

Precision medicine

The goal of precision medicine is to customize care according to each patient's unique genetic, environmental, and lifestyle variations. Future treatment for the CB1 receptor antagonist may include a tissue-specific neutral antagonist. To effectively battle insulin resistance and fat buildup, they could target skeletal muscle, adipose tissue or fatty liver[14].

Overcoming resistance

It is critical to address the psychological adverse effects that have historically been linked to CB1 receptor blockers such as rimonabant. The current approaches focus on creating peripherally restricted ligands and neutral antagonists that restrict brain entry and lower Psychiatric risk[17]. Furthermore, improving the new CB1 receptor antagonist chemical structure increases its bioavailability and binding affinity, perhaps resolving the resistance issue with the previous generation[32].

Challenges in drug development and the regulatory path

The design and regulatory clearance of new Cannabinoid 1 (CB1) receptor blockers for treating metabolic disorders face numerous challenges. The following are the main challenges.

Clinical Trial Design and Execution

A clinical trial must be properly planned to evaluate the safety and effectiveness of CB1 receptor blockers. Because of the unique mechanism of CB1 blockers and their diverse effect on metabolic pathways, the traditional trial model might not be appropriate. To forecast pharmacokinetic characteristics and spot possible drug-drug interactions early in the development phase, contemporary methods like physiologically based pharmacokinetics modelling are required[33].

Regulatory Compliance and Standard

A clinical trial must be properly planned to evaluate the safety and effectiveness of CB1 receptor blockers. Due to the unique mechanism of CB1 blockers and their diverse effects on metabolic pathways, traditional trial models may be inadequate. Contemporary approaches, such as physiologically based pharmacokinetic modelling, are needed to predict pharmacokinetic properties and identify potential drug–drug interactions early in the development process[34]. Harmonisation of standards, as seen in other industries like nanomedicine, is critical for smooth regulatory navigation[35].

Safety and Side Effect Management

Due to serious psychological adverse effects, earlier CB1 receptor blockers, such as rimonabant, were discontinued. A novel chemical must target the peripheral receptor and minimise CNS penetration in order to lower such danger. This calls for a thorough safety evaluation at the molecular level, an area where regulatory coherence is still lacking[36].

Multi-Regional Clinical Trial

There are logistical, ethical and statistical difficulties when conducting clinical trials in several regions. To promote international cooperation and accelerate drug availability, regulators and sponsors must guarantee that trials are carried out consistently using compatible methodology and shared data standards[34].

Market and Investment Consideration

It can be difficult to get funding and market interest for novel CB1 receptor blockers. Because metabolic disorders are rare or have a history of failure, pharmaceutical companies may be wary. Offering incentives, such as extended patent protection or an accelerated approval process for promising treatments, are two strategies to encourage investment[37].

Patient Engagement and Real world Data

Using real-world data to guide both development and regulatory submission is essential, as is involving patients in the drug development process. Incorporating real-world efficacy and safety data into innovative trial design can improve patient engagement and expedite the approval process[38]. Successfully navigating the complex development of CB1 receptor blockers for managing metabolic disorders requires coordination among key parties, including biopharmaceutical firms, research centres, regulatory agencies and patient communities.

CONCLUSION

The cannabinoid type-1 receptor (CB1) is a key molecular target in the pathophysiology of metabolic diseases such as obesity, type 2 diabetes mellitus, dyslipidemia, and hypertension, as there is extensive evidence to indicate that dysregulation of the peripheral CB1 receptor's expression contributes to insulin resistance, lipid metabolism, inflammation and glucose homeostasis. Additionally, the lack of clinical usefulness of the initial centrally acting CB1 receptor antagonist is due to the presence of serious adverse effects associated with the nervous system, despite there being significant metabolic benefits.

The second generation blockers, like rimonabant withdrawal, which was a shift in the field and led to the design of peripherally confined CB 1 receptor blockers. These new generation compounds are intended to have a selective action with CB 1 receptor in tissues of Metabolic activity, and minimal exposure to the central nervous system. Their preclinical activity has been strongly demonstrated in terms of enhancement of insulin sensitivity, inhibition of body weight increase, regulation of lipid metabolism and suppression of chronic inflammation in the absence of psychiatric toxicity.

New developments in the field of pharmacology design, such as limited blood-brain barrier Permeability, tissue–specific receptor–targeting, and optimization of ligand library, have made a significant contribution to the therapeutic profile of CB1 antagonist. Moreover, the new opportunities, such as combination Therapies, precision medicine and better clinical trial methods, have the potential to overcome the past drawbacks and improve clinical outcomes.

In summary, peripheral selective CB1 receptor antagonists represent a metabolically valid and clinically plausible therapy for metabolic disease. To realise the therapeutic benefit of CB1 receptor modulation and to address the increasing global disease burden attributable to metabolic disease, clinical investigations utilizing translational science, high-quality clinical trials, and regulatory alignment will be critical.

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