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PERSPECTIVE AND REFLECTION ARTICLE

Controlled downregulation of the cannabinoid CB1 receptor provides a promising approach for the treatment of obesity and obesity-derived type 2 diabetes

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Abstract Increased activity of the endocannabinoid system has emerged as a pathogenic factor in visceral obesity, which is a risk factor for type 2 diabetes mellitus (T2DM). The endocannabinoid system is composed of at least two G-protein-coupled receptors (GPCRs), the cannabinoid receptor type 1 (CB1), and the cannabinoid receptor type 2 (CB2). Downregulation of CB1 activity in rodents and humans has proven efficacious to reduce food intake, abdominal adiposity, fasting glucose levels, and cardiometabolic risk factors. Unfortunately, downregulation of CB1 activity by universally active CB1 inverse agonists has been found to elicit psychiatric side effects, which led to the termination of using globally active CB1 inverse agonists to treat diet-induced obesity. Interestingly, preclinical studies have shown that downregulation of CB1 activity by CB1 neutral antagonists or peripherally restricted CB1 inverse agonists provided similar anorectic effects and metabolic benefits without psychiatric side effects seen in globally active CB1 inverse agonists. Furthermore, downregulation of CB1 activity may ease endoplasmic reticulum and mitochondrial stress which are contributors to obesity-induced insulin resistance and type 2 diabetes. This suggests new approaches for cannabinoid-based therapy in the management of obesity and obesity-related metabolic disorders including type 2 diabetes.

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Abbreviations

2-AG	2-Arachidonoylglycerol
AEA	Arachidonoylethanolamide
CB1	Cannabinoid receptor type 1
CB2	Cannabinoid receptor type 2
CRP	C-reactive protein
CNS	Central nervous system
EC	Endocannabinoid
FAAH	Fatty acid amide hydrolase
GPCR	G-protein-coupled receptor
HbA1c	Glycated hemoglobin
MAGL	Monoacylglycerol lipase
T2DM	Type 2 diabetes mellitus
ER	Endoplasmic reticulum

Introduction

Type 2 diabetes mellitus (T2DM) is a metabolic disease with key pathological features of impaired insulin secretion from pancreatic β-cells and insulin resistance in glucose consumption and storage sites such as adipose, liver, and skeletal muscle (Ashcroft and Rorsman 2012). This metabolic disorder affects about 380 million people worldwide (Guariguata et al. 2014). Studies have linked T2DM with obesity (Bastard et al. 2006; Eckel et al. 2011), while other factors such as genetic mutations (Herder and Roden 2011), overexpression of the hormone amylin (Zhang et al. 2014), and a disturbance of the body's natural clock

(Buxton et al. 2012; Shi et al. 2013) have also been recognized as contributors to the development of T2DM. Growing evidence indicates that excessive body fat, particularly abdominal fat, can cause chronic subclinical inflammation (Donath 2014; Hameed et al. 2015; Li et al. 2015; Spranger et al. 2003; Van Greevenbroek et al. 2013). Excessive abdominal fat induces endoplasmic reticulum (ER) stress and hypertrophy in adipocytes, both of which have been associated with the production of pro-inflammatory cytokines and chemokines (Hotamisligil 2010). ER stress can also trigger an adaptive compensatory unfolded protein response (UPR) (Cnop et al. 2012; Leem and Koh 2011), which in turn leads to inflammatory processes (Hotamisligil 2008). This inflammation interferes with insulin receptor signaling through the activation of c-Jun N-terminal kinase (JNK) and subsequent serine phosphorylation of the insulin receptor substrate 1 (IRS1) (Hotamisligil 2008) and via induction of reactive oxygen species (ROS) and the activation of the nuclear transcription factor-κB (NF-κB) (Hotamisligil 2010; Zhang and Kaufman 2008). It has been demonstrated that reversal of ER stress either by genetic overexpression of ER chaperones (Kammoun et al. 2009; Ozawa et al. 2005) or administration of chemical chaperones (Özcan et al. 2006) enhanced insulin sensitivity in adipose tissue, muscle, and liver of experimental animals (Fig. 1).

The interplay of mitochondrial dysfunction and ER stress has been well documented (Leem and Koh 2011; Rieusset 2011). Imbalanced nutrient supply, energy expenditure, and oxidative respiration leads to the dysfunction of mitochondria, which contributes to the development of insulin resistance and T2DM (Goossens 2008; Lim et al. 2009; Rieusset 2011). Furthermore, obesity can lead to the expansion, hyperplasia, and hypertrophy of adipocytes, which pathologically involve ER stress, mitochondrial dysfunction, and oxidative and other cellular stress (Tripathi and Pandey 2012). Collectively, obesity-induced stress alters the secretion properties of adipocytes and leads to elevated secretion of pro-inflammatory cytokines and chemokines, such as tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), C-reactive protein (CRP), and other biomarkers of inflammation (Apovian et al. 2008; Dahlén et al. 2014; Fontana et al. 2007; Hotamisligil et al. 1995; Hotamisligil et al. 1993). These pro-inflammatory cytokines impair insulin signaling (Howard and Flier 2006; Lebrun and Van Obberghen 2008) and recruit pro-inflammatory immune cells such as macrophages to adipose tissue (Cinti et al. 2005). The infiltrated macrophages also produce pro-inflammatory cytokines, which can worsen the inflammation in adipose tissues and lead to the pathogenesis of insulin resistance (Dahlén et al. 2014; Fontana et al. 2007; Van Greevenbroek et al. 2013).

The importance of weight control has been well-established in the management of type 2 diabetes (Klein et al. 2004). Evidence from preclinical and clinical observations suggests that the endocannabinoid (EC) system is overactive in the presence of abdominal obesity and/or diabetes (Scheen 2007). Hence, attenuation of the EC system overactivity has been proposed as a new approach for the treatment of obesity and its related disorders.

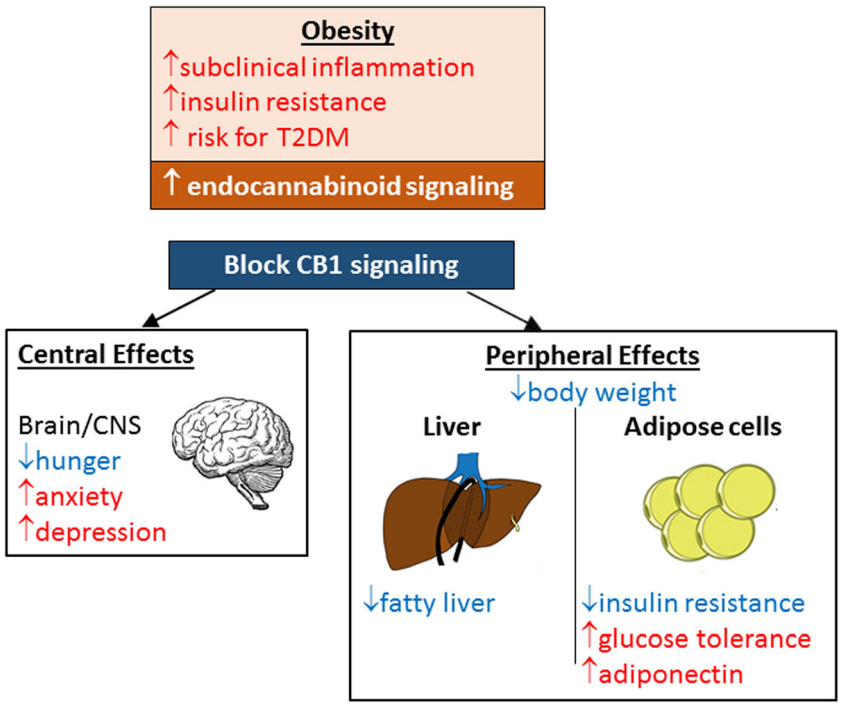

Fig. 1 The impact of blocking CB1 signaling on obesity and type 2 diabetes mellitus. Blocking CB1 signaling globally causes weight loss and decreases insulin resistance but also causes anxiogenic effects. However, blocking CB1 signaling peripherally maintains the benefits of blocking CB1 in liver and adipose cells while avoiding these anxiogenic effects

The overactive endocannabinoid system in obesity

The EC system is composed of two G-protein-coupled receptors (GPCRs), cannabinoid receptor type 1 (CB1), cannabinoid receptor type 2 (CB2), a group of lipid-derived endogenous ligands called endocannabinoids, and several metabolic enzymes that are involved in the synthesis and degradation of endocannabinoids. The endocannabinoids include arachidonoylethanolamide (AEA, anandamide) and 2-arachidonoylglycerol (2-AG) (Pertwee et al. 2010). The major physiological role of endocannabinoids is to modulate the release of neurotransmitters including excitatory amino acids (glutamate), inhibitory amino acids (GABA, glycine), and monoamines (dopamine, serotonin, noradrenaline, acetylcholine) (Di Marzo et al. 2004; Pertwee et al. 2010). The CB1 receptor possesses constitutive (also known as basal) activity in the absence of any ligand (Pertwee et al. 2010). A CB1 agonist augments the activity of the receptor above its basal level, whereas a CB1 inverse agonist decreases the activity below the basal level. A neutral CB1 antagonist has no activity, but occupies the endogenous ligand binding site to block its activity. The term "blockers" is used here to refer to antagonists or inverse agonists.

The EC system was initially known as a neuromodulatory system and has emerged as an important intercellular signaling system that regulates energy balance (Pagotto et al. 2006) and other physiological functions (Pacher et al. 2006). In general, activation of the EC system depends upon external stimuli such as cellular stress, tissue damage, or metabolic challenges (Di Marzo et al. 2004; Piomelli 2003). Experimental evidence indicates that the endocannabinoid system is chronically activated in obese states (Blüher et al. 2006; Di Marzo 2008; Engeli 2008; Engeli et al. 2005). Overactivity of the EC system may result from increased synthesis of endocannabinoids, overexpression of the cannabinoid receptors, or decreased degradation of endocannabinoids. In human obese subjects, various genetic variations of fatty acid amide hydrolase (FAAH) have been identified (Sipe et al. 2010). Genetic alteration of FAAH can lead to elevated circulating levels of AEA and other endocannabinoids (Sipe et al. 2010).

In human subjects, circulating 2-AG was correlated with body fat, visceral fat mass, and fasting plasma insulin concentrations (Cote et al. 2007). Additionally, circulating AEA and 2-AG were higher in obese menopausal women compared to lean menopausal women (Engeli et al. 2005). Increased availability of endocannabinoids may lead to an enhanced activation of cannabinoid receptors in both central nervous system (CNS) and peripheral organs (De Kloet and Woods 2009). Numerous experimental data indicate that activation of the CB1 receptor by endocannabinoids promotes food intake (Di Marzo et al. 2001), increases lipogenesis in adipose tissue and liver (Cota et al. 2003; Jourdan et al. 2012; Osei-Hyiaman et al. 2005), and induces insulin resistance and dyslipidemia (Eckardt et al. 2009; Liu et al. 2012).

Clinical evidence suggests that accumulation of abdominal fat is a critical correlate of the overactive peripheral endocannabinoid system in human obesity (Blüher et al. 2006; Cote et al. 2007). Therefore, downregulation of the overactive endocannabinoid system, particularly CB1 receptor activity, represents an attractive approach for the treatment of obesity-derived metabolic disorders such as type 2 diabetes.

Downregulation of the endocannabinoid system by CB1 receptor blockers

It has been demonstrated that downregulation of CB1 receptor activity by various CB1 inverse agonists can reduce body weight, insulin resistance, dyslipidemia, and fatty liver in obese experimental animals (Jourdan et al. 2010; Simiand et al. 1998; Trillou et al. 2003). Similar "proof-of-concept" results have been obtained from preclinical studies of CB1 receptor inverse agonists (Black 2004; Lange and Kruse 2004; Smith and Fathi 2005). In preclinical settings, activation of the CB1 receptor elicits metabolic stress conditions linked to insulin resistance and T2DM. Examples include the induction of ER stress in human and mice hepatocytes (Liu et al. 2012), impaired mitochondrial biogenesis in mice white adipose, muscle, and liver tissues (Tedesco et al. 2010), and altered hepatic mitochondrial function (Lipina et al. 2014) as well as induction of adipose hypertrophy and macrophage infiltration (Wong et al. 2012). On the other hand, downregulation of CB1 receptors by the CB1 inverse agonist rimonabant has been found to improve hepatocyte (Flamment et al. 2009) and adipocyte (Tedesco et al. 2008) mitochondrial functions, to induce transdifferentiation of white adipocytes to brown fat (Perwitz et al. 2010), and to reduce hypertrophy of adipocytes (Jbilo et al. 2005).

The therapeutic value of rimonabant, the first CB1 inverse agonist, has been assessed in multiple clinical trials (i.e., RIO Europe, RIO North America, and RIO Lipids) (Christopoulou and Kiortsis 2011). In overweight/obese non-diabetic patients, rimonabant produced significant weight loss (−4.7 to −5.4 kg) and waist circumference reduction (−3.6 to −4.7 cm). At the same time, there was a decrease in cardiometabolic risk factors (Pi-Sunyer et al. 2006; Van Gaal et al. 2005; Van Gaal et al. 2008). Along with these clinical benefits, increasing plasma adiponectin and decreasing plasma leptin and CRP were also achieved (Després et al. 2005). Adiponectin is a plasma protein exclusively secreted by adipose tissue. It induces free fatty acid oxidation, decreases hyperglycemia and hyperinsulinemia, and leads to body weight reduction (Diez and Iglesias 2003; Yamauchi et al. 2001). Data from the same clinical trials (i.e., the RIO trials) revealed that rimonabant not only can lead to significant reductions in plasma glucose and

insulin levels but can also prevent or reverse progression of glucose intolerance in overweight/obese non-diabetic patients (Scheen 2007). Clinical assessment of rimonabant in drug-naive type 2 diabetic patients has shown that the drug at a 20-mg dosage reduced HbA1C (glycated hemoglobin) and fasting plasma glucose levels, while body weight, waist circumference, and cardiometabolic risk factors were decreased (Iranmanesh et al. 2006; Rosenstock et al. 2008). Furthermore, rimonabant was investigated in overweight/obese type 2 diabetic patients who were insulin-treated or on metformin or sulphonylurea monotherapy. In this trial, reduction of body weight and HbA1c were achieved, while lipid profiles were improved (Hollander et al. 2010; Scheen et al. 2006). The clinical efficacy of rimonabant and several follow-up CB1 inverse agonists (Janero and Makriyannis 2009) in the management of body weight indicated an exciting path for the translation of CB1 receptor blockers into antiobesity and antidiabetic medications. However, soon after the regulatory approval of rimonabant in Europe, the drug was found with psychiatric side effects such as anxiety, depression, and suicidal ideation (Christensen et al. 2007; Moreira and Crippa 2009). These untoward psychiatric side effects of rimonabant caused all CB1 inverse agonists to be abandoned from further clinical development (Janero and Makriyannis 2009). However, the clinically tested CB1 inverse agonists all are CB1 blockers that can target CB1 receptors located in both central circuits and in peripheral organs (Janero and Makriyannis 2009). Given that the modulation of food intake and feeding behavior by the EC system was initially attributed to both central (Cota et al. 2003; Di Marzo and Matias 2005) and peripheral (Cota et al. 2003; Gómez et al. 2002) mechanisms, the metabolic benefits from rimonabant or other clinically tested CB1 inverse agonists cannot be exclusively ascribed to the CB1 receptors present in central circuits. The involvement of the downregulation of CB1 receptors present in the liver, muscle, adipocytes, and endocrine pancreatic cells cannot be excluded (Quarta et al. 2011). In this context, peripherally active CB1 blockers with limited brain penetration may be promising for the management of obesity and obesity-related metabolic disorders without the depressive side effects (Kunos and Tam 2011).

Investigations of the therapeutic benefits from downregulation of peripheral CB1 receptors have started recently. A number of peripherally restricted CB1 antagonists such as AM6545 (Cluny et al. 2010; Tam et al. 2010) and inverse agonists such as JD5037 (Chorvat et al. 2012; Tam et al. 2012) and others (Chorvat 2013; Dow et al. 2012; Hortala et al. 2010; Silvestri and Di Marzo 2012; Son et al. 2010; Wu et al. 2011) have provided proof of concept in preclinical studies. For instance, in mice with genetic and diet-induced-obesity (DIO), AM6545 at the dose of 10 mg/kg/day led to a 12 % weight reduction as compared to rimonabant, which caused a 21 % reduction at the same dose. Interestingly, AM6545 does not show an anxiogenic effect, which is prophetic for the neuropsychiatric side effects of centrally active CB1 inverse agonists like rimonabant (Tam et al. 2010). As a glycemic control, AM6545 is almost as efficacious as rimonabant in improving glucose tolerance and insulin sensitivity, reversing fatty liver, and improving the plasma lipid profile of the experimental animals. These effects were attributed to the blockade of CB1 receptors in peripheral tissues, as proven by the use of hepatic CB1-deficient mice (Tam et al. 2010). Similarly, the peripherally restricted CB1 inverse agonist JD5037 was demonstrated to elicit effects of reducing food intake, body weight, and adiposity without anxiogenic effects in mice models (Chorvat et al. 2012; Tam et al. 2012). Collectively, these preclinical results indicate that blockade of peripheral CB1 receptors may be sufficient to produce antiobesity effects without CNS liabilities. In addition to the effects of reducing food intake and body weight, downregulation of CB1 receptor activity by CB1 inverse agonists has been found to suppress insulin hypersecretion under conditions of metabolic dysfunction (Getty-Kaushik et al. 2009; Lynch et al. 2012; Rohrbach et al. 2012) and to promote the proliferation and survival of β-cells in pancreases of obese animal models (Doyle et al. 2011; Duvivier et al. 2009; Janiak et al. 2007; Jourdan et al. 2013; Kim et al. 2012). These effects probably resulted from the reduction of lipotoxicity, which has been implied to cause β-cell death in rodents and humans (Unger and Orci 2001).

Besides peripherally active CB1 inverse agonists, a novel class of CB1 ligands has been discovered in the last few years. This class of compounds can allosterically modulate the activity of the CB1 receptor through a site topographically distinct from the endogenous ligand binding site (Ross et al. 2012). One of these CB1 allosteric modulators, PSNCBAM-1, was characterized as an allosteric CB1 antagonist (Horswill et al. 2007). It interacts with the CB1 receptor at a receptor site that is different from the active site where traditional CB1 inverse agonists bind. The compound was demonstrated to induce acute hypophagia and weight loss in male Sprague–Dawley rats (Horswill et al. 2007). Whether the hypophagic effects from allosteric CB1 antagonists can be achieved in obese models and translated into therapeutic implications for obesity and T2DM remains to be investigated.

Conclusions

Obesity-provoked subclinical inflammation is pathogenic for insulin resistance, which is a hallmark of type 2 diabetes. Overactivation of the endocannabinoid system has been found to underpin factors of obesity. The antiobesity efficacy and metabolic benefits from blocking the CB1 receptor have been confirmed by numerous preclinical studies and multiple clinical trials of rimonabant and other CB1 inverse agonists.

However, the psychiatric side effects of globally active CB1 inverse agonists like rimonabant prevent clinical applications of this class of compounds. Alternative approaches to downregulate the endocannabinoid system by selectively blocking the CB1 receptor in the peripheral tissues have been demonstrated in preclinical studies as a viable strategy to avoid CNS side effects while maintaining therapeutic benefits. New approaches to downregulate CB1 activity through allosteric modulation are also emerging. Collectively, controlled downregulation of CB1 activity could provide a promising strategy to treat obesity and obesity-related disorders such as type 2 diabetes.

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