The endocannabinoid system: A new pharmacological target for obesity treatment?

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Abstract: Being a great threaten for human health, obesity has become a pandemic chronic disease. There have been several therapeutic treatments for this social health issue, including diet and exercise therapy, medication and surgery, among which the diet is still the most common way. However, none of these therapeutic measures available is ideal, making it necessary to find an effective medical treatment. The endocannabinoid system, which is well known for its contributions in certain mental processes such as relaxation, amelioration of pain and anxiety, and sedation initiation, has been recently reported to play an essential role in regulating appetite and metabolism to maintain energy balance, leading to the belief that endocannabinoid system is closely related to obesity. This new discovery deepens our understanding of obesity, and provides us with a new direction for clinical obesity treatment. Rimonabant is an antagonist for CB₁, and has entered the market in some countries. However, although effective as an anti-obesity drug, rimonabant also causes obviously adverse side-effects, thus is being doubted and denied for medical usage.

Keywords: obesity; weight loss; endocannabinoids; cannabinoid receptor; cannabinoid CB₁ receptor antagonist; anti-obesity agents; rimonabant

As a chronic disease with multi-pathogenesis and a variety of complications, obesity is characterized by excess accumulation of body fat, as measured by “body-mass index” (BMI), for which the body weight of an individual is divided by the square of his height. According to the definition made by World Health Organization (WHO), one whose BMI is within the range of 25-29.9 kg/m² is defined as overweight, while within the range of 30.0-39.9 kg/m² is defined as obesity, and one whose BMI is 40 kg/m² or above is

considered as morbid obesity. In the past, overweight and obesity were considered as health concerns only in developed countries. However, with the development of living qualities, more and more people, especially the young, tend to get obesity in both developed and developing countries, and their health is endangered^[1,2]. In 1999, obesity was officially documented as a preventable disease by WHO, and it has become the second lethal risk for human life following smoking. Obesity, together with AIDS, drug addiction and alcohol abuse, is considered the four major worldwide medical issues.

1 The complications and available treatments for obesity

Obesity is a high-risk factor of cardiovascular diseases, diabetes, musculoskeletal disorders and certain cancers. As

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BMI rises, the incidence of obesity complications increases gradually. While existing evidence suggests that abdominal obesity, but not BMI, is a major risk factor of metabolic syndrome, it is proposed that waist circumference is a better indicator of chronic diseases than BMI^[2].

Excess energy intake or reduced energy consumption can lead to accumulation of body fat cells that secrete a variety of adipokines, which are involved in insulin resistance, endothelial dysfunction and atherosclerosis. This can help explain the phenomenon that excess body fat accumulation is accompanied not only by impaired glucose tolerance, but also by dyslipidemia, mild chronic inflammation and hypertension. So it's believed that prevention and treatment of obesity and its related complications would also efficiently improve levels of blood sugar, lipids, pressure and C-reactive protein. And related research showed that 5%-10% loss of body weight significantly improved the lipid profile, insulin sensitivity and endothelial function, and reduced thrombosis, productions of inflammatory substances, as well as the incidence of complications^[3,4].

The current available treatments for obesity include diet and exercise therapy, medication and surgery, and the first one remains the most common. However, it's always easy to lose weight at a moderate level but very hard to keep, as proved by the report that weight loss typically peaks 6 months after treatment; however, by the end of the year, one third of the lost weight has been regained, and usually all the lost weight is regained within 5 years^[4,5]. That is, lifestyle intervention seldom works well. Meanwhile, no obesity treatment has been approved by FDA, although a handful of approved medications for illness other than obesity, such as topiramate, zonisamide, bupropion and metformin, have been found to reduce body weight^[4]. As mentioned above, challenge still exists on obesity treatment, since no available treatment is effective or safe enough, while obesity is becoming a worldwide health problem. Recent studies have found that the endocannabinoid system plays a crucial role in appetite regulation, energy consumption, as well as in lipid and glucose metabolism, attracting more concentrations in this system and also providing a possible target for clinical obesity treatment^[1,4].

2 Endocannabinoid system

The utilization of *Cannabis* plant and its extracts to alleviate symptoms of gastrointestinal disease and to promote appetite began centuries ago. In the early 1960s, Δ^9 -tetrahydrocannabinol (Δ^9 -THC) was identified as the major psychoactive component of *Cannabis*. And nearly thirty years later, the identifications and cloning of two cannabinoid receptors, CB₁ and CB₂, both of which belong to G protein-coupled receptor family, shed a light on discovering the mechanism of how Δ^9 -THC gave rise to its cellular actions. Later studies discovered the endogenous ligands of CB₁ and CB₂, as well as their related physiological effects and molecular mechanisms, arousing increasing interests in endocannabinoid system (ECS).

ECS comprises two cannabinoid receptors, CB₁ and CB₂, whose endogenous ligands were named endogenous cannabinoids (ECs), and enzymes, that are responsible for the biosynthesis or degradation of ECs^[6,7]. Cloned in 1991, the CB₁ receptor was thought to be abundant in the central nervous system, as well as in different peripheral tissues and organs such as adipocytes, hepatocytes, skeletal muscle, endothelial cells and gastrointestinal tract, whereas the CB₂ receptor cloned in 1993 was mainly expressed in cells and organs of immune system^[4]. Endogenous ligands for these receptors are identified and characterized as derivatives of the polyunsaturated fatty acid or arachidonic acid (AA), produced from cell membranes when needed through activations of their synthetic enzymes. The endogenous ligands are different from other neurotransmitters that are stored within intracellular vesicles. The most frequently studied endogenous ligands are anandamide (*N*-arachidonylethanolamine, AEA) and 2-arachidonoylglycerol (2-AG)^[6]. Their three-dimensional structures are very similar to that of THC, and they act with CB₁ and CB₂ receptors with different affinities. 2-AG mainly acts with CB₂ receptor and has a low affinity to CB₁ receptor, whereas low doses of AEA exerts its role mainly through CB₁ receptor^[8,9].

Enzymes responsible for the formations of AEA and 2-AG from their direct biosynthetic precursors include the *N*-acyl-phosphatidyl-ethanolamine-selective phospholipase D

(NAPE-PLD) and the *sn*-1-selective diacylglycerol (DAG) lipases (DAGL- α and - β), respectively. *N*-arachidonoyl-phosphatidyl-ethanolamine (NArPE) is converted into AEA by NAPE-PLD, although some alternative pathways might exist during this process. For endocannabinoid metabolism, the amidase, fatty-acid amide hydrolase (FAAH), catalyzes the hydrolysis of AEA and 2-AG. Monoacylglycerol lipases also play a major role in the enzymatic hydrolysis of 2-AG. Endocannabinoid biosynthesizing and degrading enzymes have been identified not only in the brain, but also in peripheral tissues, including the pancreas, adipose tissue, white adipocytes and rat insulinoma cells.

ECS, which has been identified as a neuromodulatory system, is believed to be relatively silent under normal conditions and assist in several psychotropic and physiological processes such as enabling relaxation, relieving pain and anxiety, initiating sedation and accumulating intra-abdominal fat when activated. Once ECS is overstimulated, numerous metabolic pathologies would occur^[10]. The functions and regulatory mechanisms of ECS are complicated and yet not fully understood, although growing evidences suggest that ECS plays an essential role in appetite regulation and metabolism to maintain energy balance.

3 ECS and obesity

3.1 Abnormal levels of ECS in obesity The evidence suggests that obesity is closely related to the hyperactivity of ECS in the body. On one hand, it's well known that high-fat diet is an important factor leading to obesity based on the report that ω -6 polyunsaturated fatty acid (precursor of ECs in the body), which can lead to an over-production of ECs, was significantly increased after the intake of high-fat diet^[10,11]. On the other hand, ECS is found to be over-activated in both animal experiments and human trials under obesity conditions, and ECs levels are higher than that in subjects with standard diet or that in normal subjects^[1,9,12]. Taken together, these findings reveal a close association between fat mass and EC levels.

The experimental results published are summed up in Table 1, suggesting that the dysregulation of peripheral ECS in mice following a prolonged high fat diet could lead to

hyperglycemia or obesity.

In rodent obesity model, EC levels in the hypothalamus and uterus are higher than normal level. However, all these animals for study are genetically absent in either leptin or its receptor, which is rare in human. Treatment with rat leptin could revert EC to normal levels in both brain and uterus, suggesting that leptin may be a negative regulator of EC^[12].

Engeli and his colleagues^[13] measured levels of circulating ECs in 20 obese and 20 lean women who were postmenopausal. Results showed that in obese subjects, levels of AEA and 2-AG were 35% and 52% higher, respectively, compared with that in lean subjects. Furthermore, this study revealed a strong negative correlation between concentration of fatty acid amide hydrolase (the enzyme that degrades AEA) and circulating levels of EC, suggesting that the increase in circulating EC levels in obese individuals may be attributable to reduced levels of degrading enzymes. Report of Monteleone *et al.*^[14] confirmed that AEA level was significantly increased in women with binge-eating disorder, supporting Engeli's conclusion in some way. Besides, Sipe *et al.*^[15] investigated the genotypes in 2667 black, white and Asian subjects, and revealed that the defective FAAH encoding gene was closely associated with obesity in both white and black subjects. Moreover, in white and black subjects, the defective genotype tended to appear more frequently in those with increased body mass index categories of overweight and obesity, which also strongly suggested an association between obesity and missense polymorphism of *faah* gene.

3.2 ECS and food intake The regulation of food intake depends on two major categories of signals that arise in the periphery and regulate food intake in the brain. For one category from the gut, a series of peptides and enzymes are secreted during digestion, and satiety signal is transferred to the brain primarily through the vagus nerve by stimulating receptors on afferent fibers. The other category is adiposity signal. Leptin secreted from adipocytes and insulin from islet β cells enter the brain, and then body fat content is signaled via circulation. All these signals are integrated in the hypothalamus to control diets and ultimately to regulate body fat content^[10].

3.2.1 ECS and satiety signal Cholecystokinin (CCK) is the

Table 1. The effects of high fat diet (HFD) on EC levels in various tissues in mice involves metabolic disorders and the potential consequences in various aspects^[9-12]

Site of Action	Effect of CB ₁ Activation	Effects of HFD	Potential Consequences
Hypothalamus	↓ Food intake	↑ ECs	↑ Body weight/ Waist circumference
Visceral adipose tissue	↑ Lipogenesis (FAS) ↑ Glucose uptake ↓ AMPK activity ↓ Adiponectin	↑ ECs	↑ Energy storage ↑ Dyslipidemia ↑ Insulin resistance ↑ Waist circumference
Subcutaneous adipose tissue	↑ Lipogenesis (FAS) ↑ Glucose uptake ↓ AMPK activity ↓ Adiponectin	↑ ECs	↓ Subcutaneous fat ↑ Visceral and ectopic fat
Brown adipose tissue	↓ Uncoupling protein-1 ↓ Futile cycle	↑ ECs	↓ Thermogenesis ↓ Energy Expenditure
Gastrointestinal tract	↓ Satiety ↑ Food assimilation	↓ Anandamide	↓ Ghrelin?
Liver	↑ Lipogenesis	↑ ECs ↑ CB ₁	↑ Dyslipidemia ↑ Dyslipoproteinemia ↑ Steatosis
Pancreas	↑ Insulin release	↑ ECs	↑ Hyperinsulinemia
Skeleton muscle	↓ Glucose uptake ↓ Glucose oxidation	↑ ECs ↑ CB ₁	↑ Insulin resistance ↓ Energy Expenditure
Heart	↑ Lipogenesis?	↑ ECs	↑ Pericardial fat ↑ Cardiovascular risk
Kidney	↑ Lipogenesis? ↓ Glomerular filtration	↑ ECs	↑ Perirenal fat? ↑ Cardiovascular risk
Thyroid	↓ Thyroid hormone	↓ ECs	↑ Metabolic rate
Adrenal glands	↓ Adrenaline release	↑ ECs	↑ Lipolysis (early) ↓ Lipolysis (late)

↑: increase, stimulation or up-regulatory; ↓: decrease, inhibitory or down-regulatory; AMPK: adenosine monophosphate-activated protein kinase; CB₁: cannabinoid-1 receptor; ECs: endogenous endocannabinoid; FAS: fatty acid synthase; HFD: high fat diets; ?: in dispute.

best-known satiety signal, and it is secreted during meals from neuroendocrine secretory cells that line in the intestinal lumen. Other peptides secreted from the gut also contribute to satiety signal, including glucagon-like peptide-1, peptide YY, enterostatin, glucagons, glucose-dependent insulinotropic peptide (GIP), pancreatic polypeptide, oxyntomodulin, and so on. In the absence of input from the hypothalamus and

other forebrain areas, the combination of these signals in the nucleus tractus solitarius (NTS) and in the hindbrain is sufficient to stop an ongoing meal in general. However, this effect is suppressed when ECS is over-activated. Research shows that EC receptors also populate the same nerves that transport satiety signals to the brain and their expressions can be inhibited by the release of CCK. In turn, ECs stimula-

tion weakens the effect of satiety signal that reduce food intake^[6,10,16].

3.2.2 ECS and adiposity signal Leptin and insulin are the best-known adiposity signals, and their receptors are expressed on neurons in brain involved in energy intake. Both of them enter the brain via circulation and contribute to reduced energy intake at the hypothalamus level. In the hypothalamus, the neural loop which controls the energy balance can be divided into catabolic and anabolic systems. When leptin and insulin reach the arcuate nucleus of the hypothalamus, they stimulate the catabolic loop and inhibit the anabolic one, resulting in appetite suppression, including reduction in food intake and increase in energy expenditure. This is supported by the research that direct administration of insulin or leptin into the brain reduces food intake, whereas lack of them leads to an opposite effect and even obesity under long-term deficient conditions^[17].

ECs and their receptors are expressed in the whole ventral hypothalamus, especially in the arcuate nucleus, and in other brain regions that control metabolism and maintain energy balance. In the hypothalamus, ECs stimulate anabolic loop and inhibit catabolic one, whereas leptin specifically reduces the activities of ECs. Di Marzo and his colleagues^[18] administered mice with leptin, and after 30 minutes they detected a significant decrease of both AEA and 2-AG by 40% and 50%, respectively, confirming that the increased leptin level through extrinsic pathway can significantly reduce EC level in the hypothalamus. Jamshidi and Taylor^[19] demonstrated the role of EC signal in the hypothalamus in another way. By injecting AEA directly into the ventromedial hypothalamus of presatiated rats and detecting their food intake within 3 hours, they observed that at some doses, these rats were apparently hyperorexia, suggesting that AEA in the hypothalamus plays a positive role on appetite. Di Marzo *et al.*^[18] observed that elevated EC levels in the hypothalamus and defective leptin signals are interrelated in obese individuals. They also found that mice deficient in CB₁ receptors ate less than their wild-type counterparts under the condition of food restriction. Besides, by administering the CB₁ antagonist, the food intake of restricted mice was reduced to that observed in mice lacking CB₁ receptors, implying that overeating re-

sponse in the physical state relies on EC activity. All these results indicate that in normal states, hypothalamic ECs increase food intake by stimulating CB₁ receptors, playing an important role in the neural network regulation of appetite.

3.3 ECS and metabolism ECS exerts its physical effect through two pathways: the central pathway and the peripheral pathway. Investigations on the animal model of obesity revealed a transient reduction of food intake but a lasting weight loss and improved metabolism, when CB₁ receptors were blocked by drugs or by genetical deletion, suggesting that ECS maintains energy balance not only through its control of appetite at the hypothalamus level, but also through its peripheral effects^[20].

3.3.1 The role of ECS in adipocytes Produced by adipocytes, adiponectin can improve insulin sensitivity and fatty acid oxidation, and decrease levels of blood glucose and plasma insulin, thus reduce the body weight. And its level decreases as weight gains. Bensaid *et al.*^[21] studied the role of CB₁ antagonists and its relationship with adiponectin in animal models. After two weeks' administration of CB₁ antagonist, all the mice gained weight and showed higher hyperinsulinemia levels. Besides, the expression level of adiponectin mRNA in adipose tissue was also increased. *In vitro* treatment of CB₁ antagonist in cultured adipocytes caused higher mRNA and protein levels of adiponectin. All of these studies demonstrate that CB₁ receptors expressed in adipocytes in normal states inhibit adiponectin activity. In a compensatory research, Cota *et al.*^[22] found that administering CB₁ agonist to adipocytes could increase lipoprotein lipase activity, so that adipocytes could intake and store more fat. However, this effect could be blocked by specific CB₁ antagonist, suggesting that lipoprotein lipase activity was mediated by CB₁ receptors. In contrast, the same treatment in adipocytes from CB₁ null mice didn't cause obvious changes. All the evidences show that ECS plays an important role in regulating fat content in adipocytes and the production of adiponectin.

3.3.2 The role of ECS in hepatocytes Activations of CB₁ receptors affect fat metabolism not only by regulating adiponectin levels but also by increasing the production of fatty acid in liver. Like adipocytes, liver is also an important site of lipogenesis, in fact even more important than

adipocytes. Osei-Hyiaman and his colleagues^[23] investigated the potential role and basic molecular target of liver as a peripheral target of ECS metabolic activity and the involvement of basic molecules in liver. The results showed that activations of CB₁ receptors could induce the synthesis of lipogenic transcription factor sterol response element binding protein-1c (SREBP-1c) and its target enzymes acetyl-coenzyme A carboxylase-1 (ACC1) along with fatty acid synthase (FAS), thus increased fatty acid synthesis. Using RT-PCR method to compare mRNA expression levels of genes involved in fat metabolism in liver and adipose tissues between CB₁ knockout and wild-type mice, scientists found that expression of SREBP-1c in CB₁ knockout mice was constantly lower than that in wild-type mice. In accordance, CB₁ antagonist administration to wild-type mice increased the expression levels of SREBP-1c and its target enzymes ACC1 along with FAS, which did not happen in mice lacking CB₁ receptors.

In vitro experiments were employed to demonstrate the expressions of CB₁ receptors in hepatocytes, including RT-PCR, immunohistochemistry and western blot. Western blot showed that protein levels of CB₁ receptors in hepatocytes in wild-type mice after 3 week's high-fat diet were significantly up-regulated, compared to mice with regular diet. Similarly, in obese mice, up-regulation of CB₁ receptors expression was detected in skeletal muscle and adipose tissue. After administering high-fat diet to wild-type mice for 3 weeks, *in vivo* evaluation of fatty acid synthesis in liver after the short-term high-fat diet revealed that the basic amount of synthesized fatty acid was significantly increased compared with that in the control counterparts. However, this did not happen in CB₁ knockout mice with the same diet. In contrast, the increased fatty acid synthesis in liver following high-fat diet decreased in wild-type mice after special CB₁ antagonist rimonabant treatment. Furthermore, liver level of AEA in mice with high-fat diet was 3 times higher than that in control group^[20].

Results above indicate that at the early stage of high-fat diet induced obesity, ECS in liver is activated (both AEA and CB₁ receptors are elevated), which is essential for obesity development especially for increased lipogenesis. Also, it is suggested that CB₁ antagonist may be used not only to keep

fit, but also to effectively prevent and reverse metabolic complications of obesity.

4 Rimonabant

Although diet and exercise therapy remains the major treatment for obesity, it's hard to persist during the therapy, which makes it meaningful and attractive to explore new drugs against obesity. Currently, most drugs in the market exert their effects mainly by inhibiting intestinal absorption. ECS maintains energy balance by regulating food intake and metabolism, providing a new possible target for obesity drug therapy. As a new type of drug for losing weight and a special CB₁ antagonist for anti-obesity treatment, rimonabant has been developed by Sanofi-Aventis and marketed in European countries. Although it has not yet been approved in USA, it still gets much interest and attention^[24].

Di Marzo and his colleagues studied the effects of synthetic CB₁ antagonist rimonabant on food intake and body weight using animal models. They found that rimonabant significantly inhibited appetite and reduced body weight in wild-type mice but exhibited no effect in mice lacking CB₁ receptors^[18]. Weight loss induced by rimonabant was mainly caused by the amount decrease of visceral adipose tissue, while muscle content remains unchanged or even increased^[1,25]. It's also reported that the decrease of food intake, caused by CB₁ antagonist administration to diet-induced obese mice, is transient, whereas the weight loss is significant and long lasting, and the insulin sensitivity is apparently improved^[1]. Rimonabant can also increase expression level of adiponectin gene in adipocytes and in serum^[1,10]. These findings strongly suggest that CB₁ receptors mediate the anti-obesity effect of rimonabant.

In the human trial, researchers carried out four large-scale double-blind trials to compare the effects on subjects who had a daily medication of 5 mg, 20 mg rimonabant or placebo for one year. A sum of 6635 adults were involved in these trials, whose BMI was either over 30 kg/m², or over 27 kg/m² with dyslipidemia, type 2 diabetes or hypertension. The results showed that 5 mg daily dose of rimonabant had little effect on any observed indicator while it exerted strong effects on those not entirely dependent on body weight

reduction, including a significant weight loss and reduced waist circumference with lower levels of triglyceride, C-reactive protein, fasting glucose, postprandial blood glucose, insulin and higher level of high density lipoprotein (HDL)^[1,4,24].

Rimonabant has been greatly expected to be a new drug for losing weight. However, a few months ago, Sanofi-Aventis officially declared to withdraw this project in phase III clinical trial, since further investigations showed that greater dose of rimonabant could induce side-effects, that were more significant than the benefits in reducing body weight and inhibiting appetite. These side-effects included nausea, diarrhea, joint pain, enhancing anxiety, irritability, depression and so on.

Further modification and reconstruction of rimonabant are required to gain a higher specificity to CB₁ receptors, which may be helpful to solve the problems mentioned above. Further studies will focus on rimonabant derivatives/surrogates, or other candidates of CB₁ antagonists with no obviously adverse effects.

5 Conclusion

As a neuromodulatory system, ECS has a low activity under normal physiological conditions, and its over-activation may cause obesity and aggravate obesity related pathological symptoms. Understanding ECS's role in maintaining energy balance is helpful to realize the mechanism of obesity and find new directions of clinical obesity treatment. However, ECS functions are much stronger and more complex than expected. Besides in regulations of food intake and metabolism, ECS is also involved in control of nociceptive pain signal, immune and emotion regulation. The failure of CB₁ antagonist rimonabant in clinical trials introduces ECS as a new target for obesity treatment. Being intriguing is the theoretical feasibility to treat obesity and its metabolic syndromes by targeting any element in the ECS and endocannabinoid signaling system. However, not all the components are sufficiently well-characterized to be viable candidates for valuable drug-discovery. It is promising that further advanced investigations and understanding of the ECS's role in body weight might provide new opportunities for obesity pharmacological therapy.

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内源性大麻素系统 —— 治疗肥胖的药物新靶点

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摘要: 肥胖已成为一种世界范围内流行的慢性病, 严重危害人类健康。目前, 肥胖的治疗包括饮食、运动、用药和手术, 其中饮食和运动疗法仍然是基础。然而, 这些方法都不理想。寻找治疗肥胖的有效药物成为一种新的趋势。有研究表明, 内源性大麻素系统在调节食欲、代谢和保持机体能量平衡方面发挥着重要作用, 与肥胖的发生发展有着密切的联系。它使人们对肥胖有了更深一步的认识, 也为肥胖的临床治疗提供了新的思路。大麻素CB₁受体拮抗剂利莫那班在显示有效临床减肥作用的同时, 还有明显的副作用, 难以成为减肥新药。

关键词: 肥胖; 减轻体重; 内源性大麻素系统; 大麻素受体; 大麻素受体-1拮抗剂; 利莫那班