Endocannabinoid System and Cardio-Metabolic Risk

K Y Loh, MMed (FamMed)*, S T Kew, FRCP**

*Department of Family Medicine, **Department of Internal Medicine, International Medical University Malaysia, Jalan Rasah, Seremban 70300, Malaysia

SUMMARY

Recent research in bio-medical science has shown an integral role of endocannabinoid system (ECS) in determining cardio-metabolic risk of human body. The mechanism is mediated through binding of endocannabinoids at the CB1 receptors. The stimulation of CB1 receptor in the brain is believed to control and mediate the effects on appetite. In normal physiology, CB1 receptors activation is responsible for energy homeostasis, govern emotions and behaviors such as anxiety, fear, appetite, food and water intake. CB1 receptors also found in peripheral tissues like liver, pancreas, skeletal muscles and adipose tissues, which play an important role in lipid and glucose metabolism. Over-activation of ECS is associated with various metabolic diseases such as dyslipidemia, insulin resistance, lipogenesis, excessive weight gain and increasing intra-abdominal obesity. All these events lead to increased cardiovascular risk. Use of selective CB1 receptor blocker such as rimonabant has shown to reduced waist circumference, better glycemic control, lower triglyceride levels, raise HDL cholesterol and over all reduction in total body fat. This drug has been recommended for patients with metabolic syndrome.

KEY WORDS:
Endocannabinoid system (ECS), Metabolic, CB1 receptor, Rimonabant

INTRODUCTION

Obesity remains one of the major public health concerns today. Obesity is significantly associated with metabolic syndrome, hypertension, type 2 diabetes mellitus, insulin resistance and cardiovascular disease. There are many factors associated with weight gain, among the well known factors are genetic, sedentary lifestyle, food intake and underlying endocrine diseases. Over the past two decades many bio-medical research were conducted to study the pathogenesis and bio-mechanism leading to obesity and metabolic syndrome. Among the most recent discoveries in this field is the endocannabinoid system (ECS) in the human body which accounts for many of the pathophysiological changes related to obesity and metabolic syndrome[1]. It is now believed that the ECS plays an integral role in determining cardio-metabolic risk of human body[1,2].

What is endocannabinoid?

The term "cannabinoid" takes its name from *Cannabis sativa,* or more commonly known as cannabis plant. For many years, drug addicts who abused cannabis were found to crave for food, gain weight and feel thirsty[3]. The research on this phenomena led to the discovery of cannabinoid receptors CB1 and CB2 in 1990s,[4] and later the discovery of endogenous molecules that are capable of binding to cannabinoid receptors with high affinity. Subsequently these endogenous substances were known as endocannabinoids in 1995[4]. Currently three type of cannabinoids compounds are present: First, the natural herbal cannabinoids from the cannabis plant, then the endogenous cannabinoids of human tissue and finally synthetic cannabinoids[5,6].

Endocannabinoid in the human body are synthesized from membrane-derived phospholipids. The two most important and commonly studied endocannabinoids are anandamide (arachidonoyl ethanolamide) and 2-arachidonoylglycerol[1,4,7]. They are highly lipophilic, act on demand and their physiological effects arise from high binding affinity to CB1 and CB2 receptors [5,6,7]. The major sites of CB receptors are the brain tissues, but other tissues and organs that play a role in metabolism of energy (especially glucose and lipids) such as adipose tissue, liver and muscles are also found to have similar receptors[2,5].

Endocannabinoid system and its physiological role

The ECS is a complex metabolic pathway comprising three components: The CB receptors, the endocannabinoids molecules, the synthesis and activation of endocannabinoids and a complex endogenous signaling system involving the neuro-endocrine system[6,7].

The stimulation of CB1 receptor in the brain is believed to control and mediate the effects on appetite. The ECS also interacts with the mesolymbic dopaminergic system which promotes food searching. Besides the central mode of controlling appetite, ECS also acts peripherally. Nerves terminal at the gastrointestinal tracts which are responsible for satiety signally were found to have CB1 receptors[2].

Many physiological studies showed that the endocannabinoid system particularly the CB1 activation, is responsible for energy homeostasis, governs emotions and behaviors such as anxiety, fear, appetite, food and water intake[4,8]. It is postulated that stressful events activate the endocanabinoid system which lead to increase satiety, pain reduction and relaxation (Table I). This phenomenon is viewed as a physiological consequence of stress and the mechanism to replenish energy[9]. The physiological mechanism of ECS is mediated through CB1 receptors at the peripheral tissues such as the liver, skeletal muscles, gastrointestinal tract, pancrease and adipose tissue[11,12].

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Corresponding Author: Loh Keng Yin, Department of Family Medicine, International Medical University Malaysia, Jalan Rasah, Seremban 70300, Malaysia
Email: Kengyin_loh@imu.edu.my

In more recent studies, both glucose metabolism and lipogenesis are also found to be regulated by this system. This has led to the new discovery of pharmacological intervention for cardio-metabolic diseases [8,9].

Other functions of this system include inhibiting hypothalamic-pituitary-adrenal functions, modulating fertility, [2,5] regulating the immune reaction and pain response [10].

Endocannabinoid system and cardio-metabolic risk

The effects of ECS stimulation both at central nervous system and peripheral tissues lead to various metabolic effects that increase cardio metabolic risk. (Table II) Obesity is one of the major concerns in ECS over stimulation. Recent research data has shown an association between peripheral ECS and human obesity whereby the circulating endocannabinoids in the blood are at higher levels in obese than in slim women[13,14].

Of the different sites of adipose tissue in the body, intra-abdominal adipose tissue is the major contributor to cardio metabolic risk[15]. With the discovery and understanding of ECS, intra-abdominal adipose tissue is considered a highly active endocrine organ[15]. Through cytokines expression, there is an increased absorption of free fatty acid in the portal circulation, and pro-inflammatory state. These events contribute significantly to abnormal glucose and lipid metabolism[2,12,13]. Intra-abdominal obesity is also related to insulin resistance, hypertension, elevated LDL, elevated triglyceride, lower HDL, prothrombotic and pro-inflammatory states[16,17,18].

The overall risk of cardiovascular death is found to be related to increased waist circumference and study has shown that waist circumference is a more powerful predictor of obesity related cardiovascular risk as compared to BMI which is commonly used[18,19]. Obesity particularly intra-abdominal fat accumulation too, has negative impact on prognosis of all cardiovascular diseases[19].

Table I: The major physiological role of ECS [4,8,9]

Reduction of pain
Reduction of anxiety
Increase in appetite
Modulation of temperature
Regulation of hormone production
Relaxation of smooth muscle tone
Extinction of aversive memory

Another important effect of ECS stimulation at the peripheral tissues is decreased levels of adiponectin and elevated levels of C-reactive protein through the expression of a number of cytokines in adipose tissues. Adiponectin is a hormone secreted by adipocytes which has both insulin sensitizing and anti-atherogenic effects and play an important role in glucose and lipid metabolism. Decreased adiponectin levels is associated with cardiovascular disease and type 2 diabetes mellitus[20,21]. Elevated C-reactive protein are signs of inflammation and it is associated with insulin resistance and increased cardiovascular risk[19,20,21].

Reduced expression of AMP kinase in the visceral adipose tissue is another associated finding. AMP kinase is an enzyme which plays a role in lipid oxidation and glucose transport. In the liver, CB1 receptor stimulation is associated with increased activity of de novo lipid synthesis and in the skeletal muscles it is associated with insulin resistance [2, 22].

Pharmacotherapy for endocannabinoid system over activity

Pharmacotherapy is now available for the treatment of ECS over activity. The first selective CB1 receptor blocker available in the market is Rimonabant. This drug has been shown in clinical trials to be associated with significant weight loss, reduction in waist circumference, improved glycemic index of diabetes patients (improve HbA1C in diabetics), lowering the triglycerides, elevate the HDL cholesterol and increase in plasma adiponectin levels[23,24,25]. In one of the latest studies in Europe, Rimonabant is also found to reduce total body adipose tissues, subcutaneous fat and visceral fat after 12 months of treatment as compared to placebo[26]. The fatty liver index (a measure of liver steatosis) and the inflammation levels as measured by C-reactive proteins was also improved and reduction in systolic blood pressure was found as compared to placebo[26]. This drug is indicated for patients with multiple cardiovascular risk such as type 2 diabetes, dyslipidemia and obesity. Major side effects of this drug are depression, anxiety, and nausea. This drug is contraindicated for those with a risk of developing depression [23,24,26].

CONCLUSION

Endocannabinoid system is a complex endogenous mechanism responsible for various metabolic diseases such as dyslipidemia, insulin resistance, lipogenesis and weight gain via the stimulation of cannabinoid receptor CB1 and CB2. Increase in intra-abdominal lipogenicity increases the overall cardiovascular risk. Selective CB1 receptor blocker

Table II: Common site of CB1 over activation and its results

A. Central nervous system (Hypothalamus)	Craving for food
B. Peripheral tissues	
Adipose tissue	Increase in lipogenesis Reduced adinopectin Reduced expression of AMP kinase Insulin resistance
Muscle	Reduced glucose up take Insulin resistance
Intestine	Reduced satiety signals
Liver	De-novo fatty acid synthesis Dyslipedimia Insulin resistance

Rimonabant has been shown in clinical trials to be effective in improving glycemic control, reducing weight and improving lipid profile. This drug has been recommended for patients with metabolic syndrome.

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MCQ (TRUE/FALSE)

1. The physiological role of endocannabinoid system include:
   A. Relaxation
   B. Regulate hormone
   C. Emotion stabilization
   D. Modulate temperature
   E. Reduce food intake

2. The following statements are true regarding endogenous cannabinoids:
   A. They are synthesized from membrane-derived phospholipids.
   B. They are highly water soluble.
   C. The receptors for endogenous cannabinoids are only found in brain tissue.
   D. They bind to CB1 receptors with high affinity.
   E. Anandamide is an example of endogenous cannabinoids.

3. Endocannabinoid system over activation lead to:
   A. Lipolysis
   B. Insulin resistance
   C. Lipogenicity
   D. Reduced satiety signals
   E. Increased glucose usage

4. Intra abdominal obesity is associated with:
   A. Insulin resistance
   B. Elevated HDL
   C. Elevated C-reactive proteins
   D. Hypertension
   E. Hypertriglyceridemia

5. The following statements are true regarding Rimonabant.
   A. It is a cannabinoid receptor 1 antagonist
   B. It is associated with reduction of waist circumference.
   C. Improves HbA1C in diabetic patients.
   D. Elevate HDL cholesterol
   E. May cause depression.