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Effect of high fat diet on appetite regulation and obesity: Endocannabinoid system pathway

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Abstract
Obesity is an public health problem leading to other metabolic diseases and its prevalance globally increasing. A disturpt in molecular regulation of appetite metabolism causes to obesity by leading to hyperphagy. Dietary pattern affects directly to appetite regulation. Therfore, dietary pattern is so important for obesity prevalance. There are many factor in appetite mechanism having complex system. One of these factors is endocannabinoid system. Over activation of endocannabinoid system relating to dietary fat pattern leads to obesity by increasing food intake. The aim of this research is to investigate effects of dietary fat pattern on obesity through endocannabinoid system.

Keywords: endocannabinoid system, obesity, nutrition, diet

1. Introduction
Obesity is an important public health problem reaching epidemic levels in all age groups around the world [1, 2]. Along with obesity, many metabolic diseases can occur, especially cardiovascular diseases [3]. Therefore, interest in pathophysiological mechanisms underlying relationship between obesity and metabolic syndrome, diabetes and cardiovascular risk and new therapeutic targets are increasing. Current researchs show that risk factors of obesity alone/in combination play role in risk development and prognosis of disease [4-6]. However, in recent years it has been implicated that a intracellular signaling system known as endocannabinoid system (ECS) plays an important role in regulation of energy balance, feeding behavior, hepatic lipogenesis and possibly regulation of glucose homeostasis. Since discovery of energy intake regulation and metabolism of ECS, some question markings for pathogenesis of obesity have been removed. Scientific evidence suggests that ECS plays an important role in development of obesity and ECS is overactive in obesity [7-9]. Moreover, it was observed that animals without cannabinoid type 1 (CB1) receptor playing role in appetite regulating and body weight were found to be weak and resistant to diet-related obesity and dyslipidemia [10]. Clinical trials examining pharmacological blockade of CB1 with rimonabant (20 mg/day) in the mid-2000s, this approach has potential to affect many cardiometabolic risk factors (fasting plasma glucose, dyslipidemia) along with abdominal obesity [11-13]. Depending on side effects such as nausea, vomiting, diarrhea, headache, dizziness, anxiety and mood changes [13], Food and Drug Administration (FDA) prevented rimonabant using in obesity treatment in 2007. In 2008, European Medicines Agency (EMEA) has stated that benefits of rimonabant are no more than risks and suggest that it should not be offered for sale [14]. These results make it necessary to clarify mechanisms underlying of factors causing development of obesity and to find more reliable and effective methods in prevention and treatment of obesity. For this reason, in this review, it is aimed to discuss based on evidence role of ECS on obesity development and effect of dietary pattern on ECS.

2. Endocannabinoid System
Endocannabinoid system was identified at the beginning of 1990's with discovery of Δ9-tetrahydrocannabinol (THC) found in *Canabis sativa* [15]. It is a physiological system activated by activation of CB1 and CB2 receptors with anandamide (AEA) and 2-arachidonyl glycerol (2-AG) endocannabinoids [16]. Relationship between ECS and some metabolic diseases, mainly obesity, depends on function of endocannabinoids and cannabinoid receptors.

2.1. Endocannabinoids
Endocannabinoids are endogenous fatty acid derivatives can bind to cannabinoid receptors (17). To date, along with AEA and 2-AG, of functions are less known N-arachidonyl dopamine (NADA), 2-arachidonyl glycerol ether (noladine ether) and O-arachidonyl ethanolamine (viroamine) endocannabinoids have been described [18] (Figure 1).

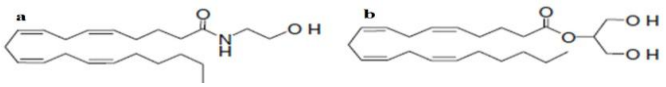

Fig 1: Biochemical structures of Anandamide (a) and 2-Arachidonyl glycerol (b) [16].

AEA and 2-AG are composed of arachidonic acid (AA) being intermediate product of linoleic acid metabolism and precursor of other regulatory lipids [19]. Linoleic acid can easily converted to AA after conversion to γ-linoleic acid, and eicosatetraenoic acid, respectively [20]. AEA is formed by addition of ethanolamide and phosphatidyl ethanolamide structures to AA accompanied with FAAH enzyme or by conversion of AA to N-arachidonoyl phosphatidyl ethanolamide accompanied with N-acyl transferase enzyme

and Ca^{2+} [21]. It is thought that NAPE is the most important resource in AEA formation [22]. 2-AG is formed by conversion of diacylglycerol structure of AA to 2-arachidonyl glycerol with diacylglycerol lipase or by conversion of phosphatidylinositol with phospholipase A1 [23]. The required enzyme is phospholipase C for conversion of phosphatidylinositol bisphosphate to diacylglycerol and lysophosphatidylinositol to 2-AG [24] (Figure 2).

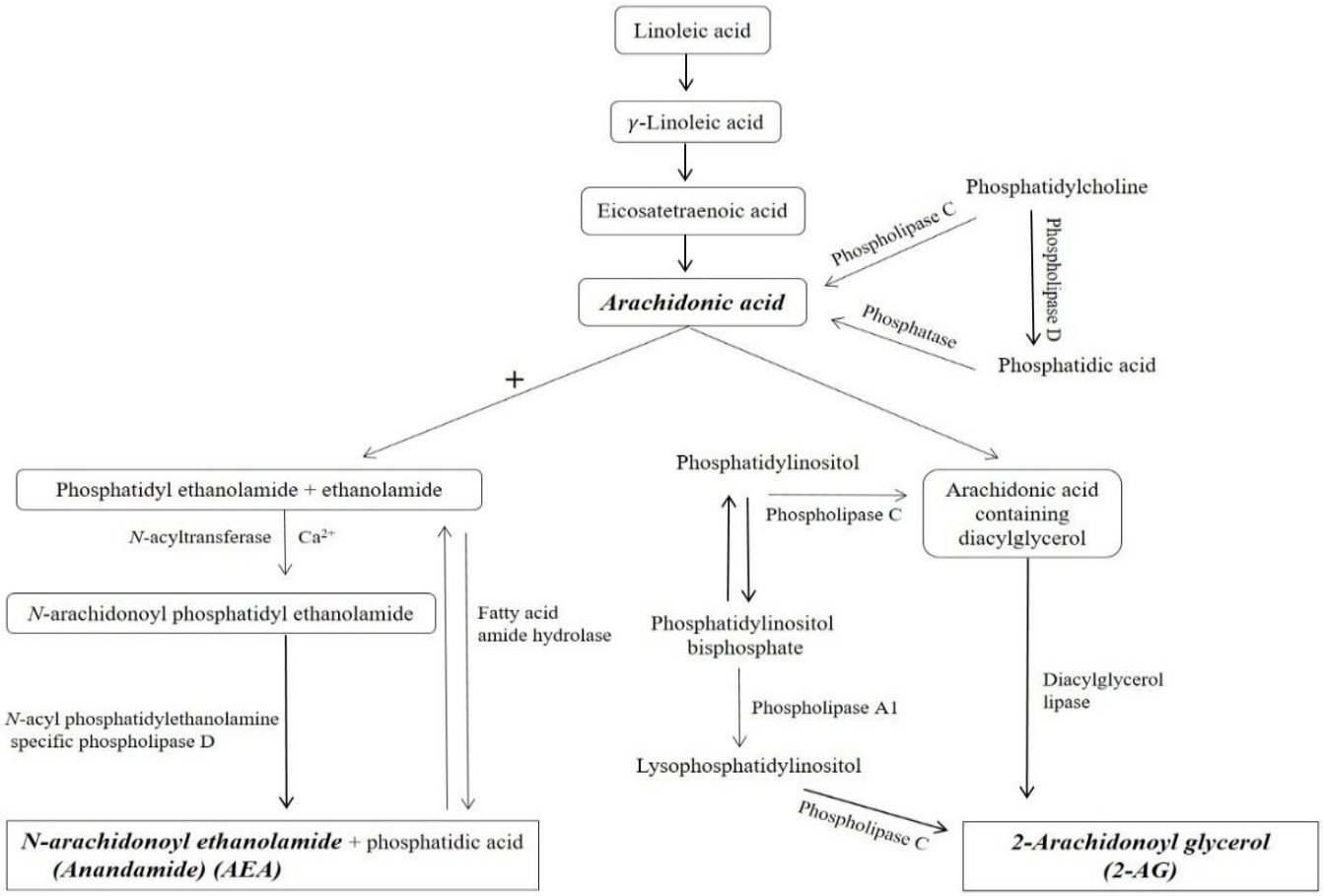

Fig 2: Main pathway of endocannabinoids biosynthesis (AEA, 2-AG) (adapted from Naughton *et al*. [25]).

Following identification of cannabinoids, cannabinoid receptors and endocannabinoids, effects of ECS on metabolic diseases, mainly obesity, have been investigated [26, 27]. As a result of studies, ECS has been shown to regulate food intake and energy balance, to have effects on appetite metabolism and to increase food intake [28, 29].

2.2. Endocannabinoid system, appetite and obesity

Hypothalamus plays an important role in regulation of important mechanisms such as energy balance, appetite, hunger-satiety [30]. Following food consumption, hypothalamus is stimulated by hormones secreted by small intestine and central nervous system signals, and satiety occurs. A disturbance in these signals or mechanisms is associated with obesity [31]. It may be evidence that later satisfied and/or to consume more food of obese than normal weight individuals.

Many orexigenic/anorexigenic hormones affect to hypothalamus. In these hormones, it is thought that ghrelin and leptin have role in mechanism of ECS on obesity [32, 33]. Moreover cholecystokinin (CCK) being small intestinal hormone and has an important role in suppressing appetite, has been shown to reduce expression of cannabinoid receptors stimulating food intake [34].

In a study by Rigamonti *et al.* [35] examined role of gastrointestinal orexigenic-anorexigenic peptides and endocannabinoids on desire to consume chocolate in obese. There was significant correlation between in ghrelin, an organsigenic hormone, and AEA/2-AG levels with chocolate consumption, but wasn't in Peptide tyrosine-tyrosine (PYY) and Glucagon-like peptide-1 (GLP-1) are anorexigenic hormones. It has been concluded that ghrelin and chemical signals such as AEA and 2-AG endocannabinoids are important in terms of nutrition and obesity and that presence of other agents antagonizing effects of these agents may be important in treatment of obesity. These results show an interesting mutual action that CCK, a satiety factor, blocks action of endocannabinoids are orexigenic [36]. Also, activation of ghrelin receptor prevented downregulation of CB1 receptors by CCK, thereby limiting extent of its action [37].

Appetite regulation and food intake control is a complex process involving neurological mechanisms [38]. ECS is

thought playing role on obesity by acting on appetite and hunger-satiety mechanisms of hypothalamus causing stimulate food intake [39]. Presence of AEA, 2-AG and CB1 receptors sensing these compounds in hypothalamic areas may be evidence this stuation. In a study on rats, it was found that injection of 50mg AEA into ventromedial hypothalamus resulted in a significant increasing in food intake by hyperphagy development. It may be from appetite stimulating action of AEA is part of stimulation of reward/rewarding-behaviour [40]. In another study, paraventricular hypothalamic nukleus was activated after 45 minutes injection of AEA [41]. Other studies also support this data [42-44]. There are studies of similar results on humans [45-47]. As a result, it is revealed that endocannabinoids increase food intake by activating CB1 receptors in hypothalamus and thus causing obesity development.

2.3. Relationship between endocannabinoid system, adipose tissue and lipogenesis

In addition to effects of ECS on appetite metabolism, studies have also been carried out to show that it is effective in some mechanisms particularly in adipose tissue and lipogenesis [48-51]. As a result of increased endocannabinoid levels, canabinoid receptors in adipose tissue are stimulated, lipid metabolism can be affected by various mechanisms, lipogenesis is increased and fatty acid β-oxidation is decreased [52]. In realization of these mechanisms, decreased production of adiponectin [8], increased lipoprotein lipase enzyme activity [48], inhibition of AMP-activated protein kinase enzyme [53] play role.

In a study of presence of endocannabinoids in adipose tissue of healthy subjects, it was found that adipose tissue can bind AEA and 2-AG, which are effective in energy balance and body weight management, and endocannabinoids can play an important role in control of adipose tissue fat mass [54]. In another study, level of AA, endocanabinoid precursor, was positively correlated with body mass index (BMI) and obesity [55]. In another study, it has been found that there is a relationship between small intestine microbiota and ECS and this plays an important role in control of adipogenesis in intestinal system and adipose tissue [56]. These results suggest that endocannabinoids may play an important role in medical treatment of obesity.

Another mechanism, thought ECS causing obesity, is to increase lipogenesis. CB1 receptor activation is known to increase lipogenesis-induced lipid accumulation in both liver [49,57] and fat cells [48, 58, 59]. Bluher *et al*. [51] investigated relationship between circulating endocannabinoid levels and adipose tissue in obese and normal body weight individuals. It was determined that 2-AG levels in circulation were correlated with body fat-mass, visceral fat-mass and fasting plasma insulin ($p < 0.05$). Moreover, there is a positive relationship between accumulation of abdominal fat and ECS in obese. As a result, it has been emphasized that there must be effective measures for inhibition of ECS in treatment and prevention of abdominal obesity and related metabolic diseases.

In a study by Annuzzi *et al*. [60] of obese with Type 2 Diabetes, obese without diabetes, and normal weight without diabetes, subcutaneous adipose tissue and AEA, 2-AG, OEA, PEA levels were investigated. It has been stated that AEA concentrations in SAT are associated with increased lipogenesis in liver and this can not be excluded from certain metabolic disorders in obese with diabetes. In conclusion that may be due to overactivation of CB1 receptors stimulated by increased AEA concentrations in SAT. Similar results were found in a study and it was found that endocannabinoid system effects energy balance and causes obesity by stimulating lipogenesis in peripheral tissues and central orexigenic pathway. Cannabinoid receptor antagonists in ECS have been shown to play an important role in prevention and treatment of obesity due to suppression of food intake and lipogenetic pathway [48].

2.4. Effects of high fat diet on endocannaniboid system

Eating behavior is regulated by two different systems, homeostatic and hedonic. The homeostatic pathway provides control of energy balance by increasing desire to eat when energy stores are empty. The hedonic pathway is a system based on award increasing desire to delicious food by surpassing homeostatic pathway when energy is excessive in body [61]. Some foods (rich in sugar and/or fat), just as addictives, have been shown to cause increased gene expression especially in nucleus accumbens and increased expression of dinofrinin, an endogenous opioid in arcuate nucleus [62]. Opioid and dopaminergic system are also effective in food enjoyment. It is known that high fat diet (HFD) increases desire to eat by stimulating hedenoic center thereby causing weight gain by distorting energy balance in positive direction [62, 63], it is expressed that HFD also increases body weight through ECS.

HFD stimulates cannabinoid receptors by increasing endocannabinoid levels. Thus, ECS becomes active and causes to increase food intake by stimulating hypothalamic regions controlling hunger-satiety and appetite mechanisms [33, 64, 65]. Given relationship between increasing food intake and increasing obesity risk (66), it can be said that ECS has an important role on development of obesity. ECS also play a role in development of obesity and other metabolic diseases by stimulating adipogenesis and lipogenesis in peripheral tissues [67, 28] (Figure 3). Therefore, endocannabinoids are thought to be a new biomarker for obesity [68].

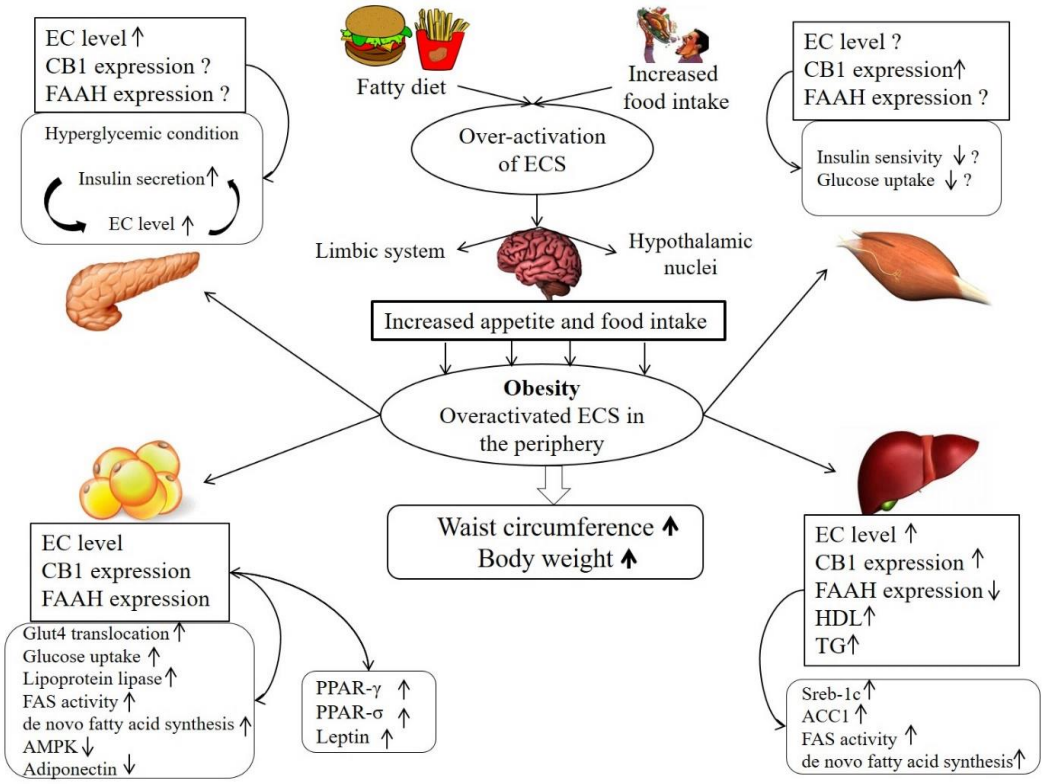

Fig 3: Relationship between endocannabinoid system, food intake and obesity (adapted from Di Marzo and Matias [65], Eckardt *et al.* [69], Vettor and Pagano, 2009 [70]). ACC1: Acetyl co-enzyme-A carboxylase-1; AMPK: AMP-activated protein kinase; CB1: Cannabinoid1; EC: Endocannabinoid; ECS: Endocannabinoid system; FAAH: Fatty acid amide hydrolase; FAS: Fatty acid synthase; Glut-4;Glucose transporter type-4; HDL; High density lipoprotein: Sreb-1c: Lipogenic transcription factor (Sterol regulatory element binding transcription factor-1); TG; triglyceride.

Since endocannabinoids are fatty acid derivatives, they are directly related to dietary pattern. Therefore, HFD may lead to the development of obesity through ECS by increasing endocannabinoid levels. Some studies examining relationship between HFD and ECS shown in Table 1.

Table 1: Effects of dietary pattern on endocannabinoids

Study-Year	Materials-Methods	Results
Engeli *et al.* 2014 [71]	Two weeks isocaloric LFD and HFD in obese and normal weight subjects.	Weight-neutral changes in dietary fat intake cannot explain excessive endocannabinoid availability in human obesity. Obesity and dietary fat intake affect ECS gene expression in a tissue specific manner.
Alvheim *et al.* 2013 [72]	Atlantic salmon were fed FO and SO for 6 months. Male C57BL/6J mice were fed diets of 35% of energy as fat based on FO- and SO-enriched salmon for 16 weeks.	Excessive dietary LA elevates endocannabinoids in the liver of salmon and mice, and increases weight gain and counteracts the anti-inflammatory properties of EPA and DHA in mice.
Crespillo *et al.* 2011 [73]	Rats were fed with two different types of diets for 12 weeks: an STD (10% fat) and an HFD (60%fat) in order to induce obesity.	The accumulated caloric intake was progressively higher in rats fed on the HFD than the STD, resulting in a divergence in body weight gain.
Alvheim *et al.* 2012 [74]	Mice were fed diets containing 1 en% LA, 8 en% LA, and 8 en% LA + 1 en% EPA+DHA in medium-fat diets (35 en% fat) and HFD (60 en%) for 14 weeks from weaning.	Dietary LA increased tissue AA, and subsequently elevated 2-AG+1-AG and AEA resulting in the development of diet-induced obesity.
Martin *et al.* 2017 [75]	Mice were fed for an additional 12 weeks the same phytol-free, phytoestrogen-free, 10 kcal% fat control chow or pair-fed isocaloric HFD.	LKO markedly diminished the impact of HFD on brain endocannabinoid levels.
Batetta *et al.* 2009 [76]	Male Zucker rats were fed for 4 weeks a control diet or diets supplemented with either FO or KO.	Diets rich in (n-3) LCPUFA, and a KO-based diet which was associated with lower endocannabinoid concentrations in several peripheral tissues.
Matias *et al.* 2008 [77]	Animals were fed for 14 weeks different HFDs are HFD1; 25.5% fat (49% of calories), 22% protein and 38.4% carbohydrate. HFD2; 33.8% fat (59.9% of	Statistically significant elevations (in the skeletal muscle, heart and kidney) or reductions (in the thyroid) of the levels of either AEA or 2-AG, or

	calories), 23.9% protein and 27.1% carbohydrate.	both, were found.
Piscitelli *et al*. 2011 [78]	1: mice was fed a normal nonpurified diet, composed of normal mice pellet; 2: mice was fed a HFD, containing 21 wt% butter-fat and 0.15 wt% cholesterol; 3-5: mice, respectively, were fed a HFD with increasing doses of KO 1.25, 2.5 or 5% wt of KO.	Eight-week HFD increased endocannabinoid levels in all tissues except the liver and epididymal AT, and KO reduced anandamide and/or 2-AG levels in all tissues but not in the liver, usually in a dependent manner.

2-AG: 2-Arachidonilglycerol; AA: Arachidonic acid; AEA: Anendamide; AT: Adipose tissue; DHA: Docosahexaenoic acid; ECS: Endocannabinoid system; EPA: Eicosapentaenoic acid; FO: Fish oil; HFD: High fat diet; KO: Krill oil; LA: Linoleic acid; LC-PUFA: Long-chain PUFA; LFD: Low fat diet; LKO: Fabp1 gene ablation; SO: Soyabean oil, STD: Standard/low-fat diet.

3. Conclusion

HFD leads to increased endocannabinoids, increased endocannabinoids cause activation of CB1 receptors by activating ECS. This stimulates hypothalamus, including hedonic system and limbic system, leading to increased food intake; stimulates of adipogenesis in adipose tissue, decreases adiponectin production, increases lipogenesis and reduces fatty acid oxidation, so it increases risk of developing metabolic diseases such as insulin resistance, Type 2 Diabetes and cardiovascular diseases, particularly obesity.

Preventing obesity increasing prevalence and reaching epidemic proportions globally, is easier and less costly than treatment. For this reason, especially regulation of amount and pattern of fat in dietary pattern is an important requirement in prevention of obesity.

Conflict of ınterest: No conflict of interest was declared by the authors.

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