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Review Article

Diet, endocannabinoids, and health☆

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ABSTRACT

Healthy aging includes freedom from disease, ability to engage in physical activity, and maintenance of cognitive skills for which diet is a major lifestyle factor. Aging, diet, and health are at the forefront of well-being for the growing population of older adults with the caveat of reducing and controlling pain. Obesity and diabetes risk increase in frequency in adults, and exercise is encouraged to control weight, reduce risk of type II diabetes, and maintain muscle mass and mobility. One area of research that appears to integrate many aspects of healthy aging is focused on understanding the endocannabinoid system (ECS) because of its role in systemic energy metabolism, inflammation, pain, and brain biology. Physical activity is important for maintaining health throughout the life cycle. The benefits of exercise facilitate macronutrient use, promote organ health, and augment the maintenance of metabolic activity and physiological functions. One outcome of routine exercise is a generalized well-being, and perhaps, this is linked to the ECS. The purpose of this review is to briefly present the current knowledge of key components of the ECS that contribute to appetite and influence systemic energy metabolism, and dietary factors that alter the responses of ligand binding and activation of cannabinoid receptors and its role in the brain. Herein, the objectives are to (1) explain the role of the ECS in the body, (2) describe the relationship between dietary polyunsaturated fatty acids and macronutrient intake and systemic metabolism, and (3) present areas of promising research where exercise induces endocannabinoid production in the brain to benefit well-being. There are many gaps in the knowledge of how the ECS participates in controlling pain through exercise; however, emerging research will reveal key relationships to understand this system in the brain and body.

Article Outline

Abbreviations: 2-AG, endocannabinoid 2-arachidonoylglycerol; AA, arachidonic acid; AEA, endocannabinoid *N*-arachidonylethanolamide or anandamide; CB1 (type 1), cannabinoid receptor 1; CB2 (type 2), cannabinoid receptor 2; DHA, docosahexaenoic acid; eCB, endocannabinoids; ECS, endocannabinoid system; EPA, eicosapentaenoic acid; PUFA, polyunsaturated fatty acid.

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1. Introduction

The endocannabinoid system (ECS) influences metabolism and physiology of multiple systems (Fig. 1). The principle action of the ECS on metabolism is anabolic, leading to protein synthesis, glycogen synthesis, and fat deposition. Activation of the ECS receptors in the brain stimulates appetite and thus, not surprisingly, leads to anabolic processes such as fat accretion. Several studies provide evidence in animal models and humans that, in conditions of obesity and hyperglycemia, the ECS is in an overactivated metabolic/physiologic state [1-3]. This response is described as a change in ECS tone or level of function supporting fat deposition and high blood glucose. The combined actions of ligands, receptors, and enzymes of the ECS for the synthesis and degradation of endocannabinoids (eCB) are in a state of overactivation stimulating appetite and anabolic conditions during obesity.

Not only does aging follow the chronological course of life, but evidence indicates that the rate of aging for biological and phenotypic outcomes is unique to the individual and influenced by genotype [4]. In general, the rate of aging of 38-year-old adults is variable and thus impacts the integrity of organ systems, cognition, and physical appearance [4]. Healthy adults of the same chronological age exhibited different rates of biological aging of strength, cognition, organ systems, and looks. Moreover, the incidence of chronic disease begins at a rapid rate as people reach 60 years and beyond, including cardiovascular disease, type 2 diabetes, as well as stroke and neurological disorders [4], so identifying approaches to delay the onset of chronic disease are of great interest. Although the pace of aging is unique to the individual and likely influenced by environment, social aspects, and lifestyle factors such as diet and exercise, the future of reversing acceleration of aging in young adults will require proper assessment tools and understanding of all factors that influence aging.

With regard to the brain, changes in the brain of mice show changes in the ECS that appear to influence the progression of aging in the brain [5]. The hippocampus is one site that is susceptible to age and neurodegeneration, and recent evidence shows that measuring eCB levels reveals differences between young and old mice. Moreover, the enzymes for the synthesis and degradation of eCB are different between young and old mice [5]. Furthermore, in rodents and humans, evidence indicates that eCB signaling

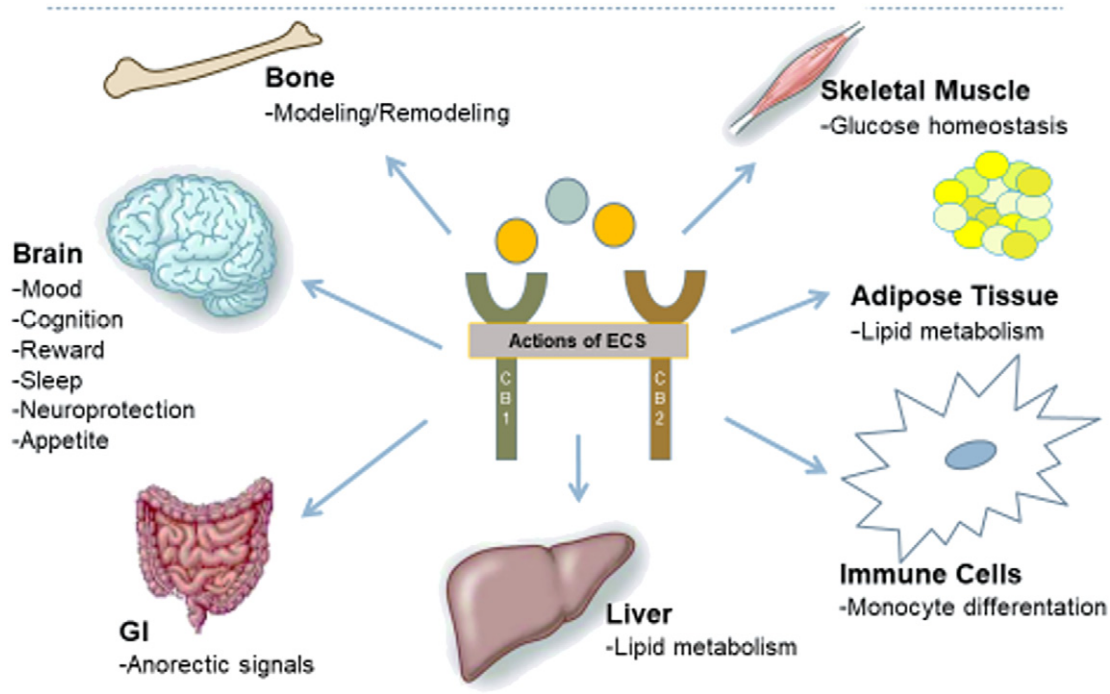

Fig. 1 – Systemic actions of the ECS. The endogenous agonists for the cannabinoid receptors (CB1 and CB2), which are synthesized from AA, an n-6 PUFA, both anandamide and 2-arachidonylglycerol, bind to both receptors. More recent work demonstrates that the n-3 PUFAs EPA and DHA can alter ECS signaling by increasing the amounts of eCB produced from the n-3 PUFA substrates.

undergoes age-dependent changes [6], which include a decline in binding of eCB to the cannabinoid receptor CB1 in rodent hippocampus and hypothalamus of older rodents. Likewise, in the human, the CB1 receptors decline in the brain of older individuals compared to the young. Thus, a key question is if lifestyle factors such as physical activity in aging adults can lead to an increase in eCB production and signaling considering that exercise has been reported to increase brain levels of eCB in rodents or blood levels in the human [7].

2. Endocannabinoids, diet, aging, and health

2.1. *Endocannabinoids in brief*

The ECS consists of ligands, receptors, and the associated biosynthetic and degradation enzymes for its ligands, the eCB. The eCB are endogenous ligands, and the most investigated are those derived from arachidonic acid (AA), both N-arachidonoyl-ethanolamine (anandamide, AEA) and 2-arachidonoylglycerol (2-AG). However, other eCB are derived from the n-3 polyunsaturated fatty acids (PUFAs) eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), which are N-eicosapentaenoylethanolamide and N-docosahexaenoyl-ethanolamide, respectively. Elevated levels of AEA and 2-AG in obese and overweight individuals have been linked to insulin resistance, dyslipidemia, and coronary artery disease [8-11]. The substrate PUFAs used for the synthesis of eCB are shown in Fig. 2.

The cannabinoid receptor named CB1 was discovered in 1990 [12], and a second receptor, CB2, followed a few years later [13]. Both CB1 and CB2 are G-protein–coupled receptors that possess 7 transmembrane domains [14], and the expression of these receptors varies considerably across tissues and cell types. CB1 is primarily located in the central nervous system, whereas CB2 is more prevalent peripherally, particularly in immunocompetent cells [15]. The relationships between the eCB, their receptors, and target organs and actions are shown in Figs. 1 and 3.

The CB1 is mainly expressed in the nervous system, with concentrated expression in specific regions of the brain in rats and humans (Figs. 1 and 3). Within the neurons, CB1 expression is associated on axons and their terminals in mouse forebrain [16]. Other tissues are found to express CB1 at different levels, for example, mouse liver [17], pancreas β cells of Swiss albino OF1 male mice [18], human and mouse primary muscle cell cultures [19,20], 2016), immune cells in rats [21], and reproductive tissues of Lister hooded male rats [22]. The CB2 receptors are found in human immune cells (such as B cells, natural killer cells, monocytes, neutrophils, CD8 T cells, and CD4 T cells) [23], human osteoclasts, and mouse calvarial osteoblasts [24]. Binding of both CB1 and CB2 receptors by their ligands leads to reduced cAMP synthesis coupled with increased potassium ion efflux and decreased calcium ion influx. In addition, the binding affinities of the eCB ligands vary between the 2 receptors. AEA has a high affinity for CB1 but a considerably lower affinity for CB2, whereas 2-AG binds to both receptors.

The biosynthesis for AEA and 2-AG is catalyzed by 2 different enzymes, N-arachidonoyl phosphatidylethanolamine phospholipase D for AEA and diacylglycerol lipase for 2-AG [25]. The enzymes responsible for the degradation of

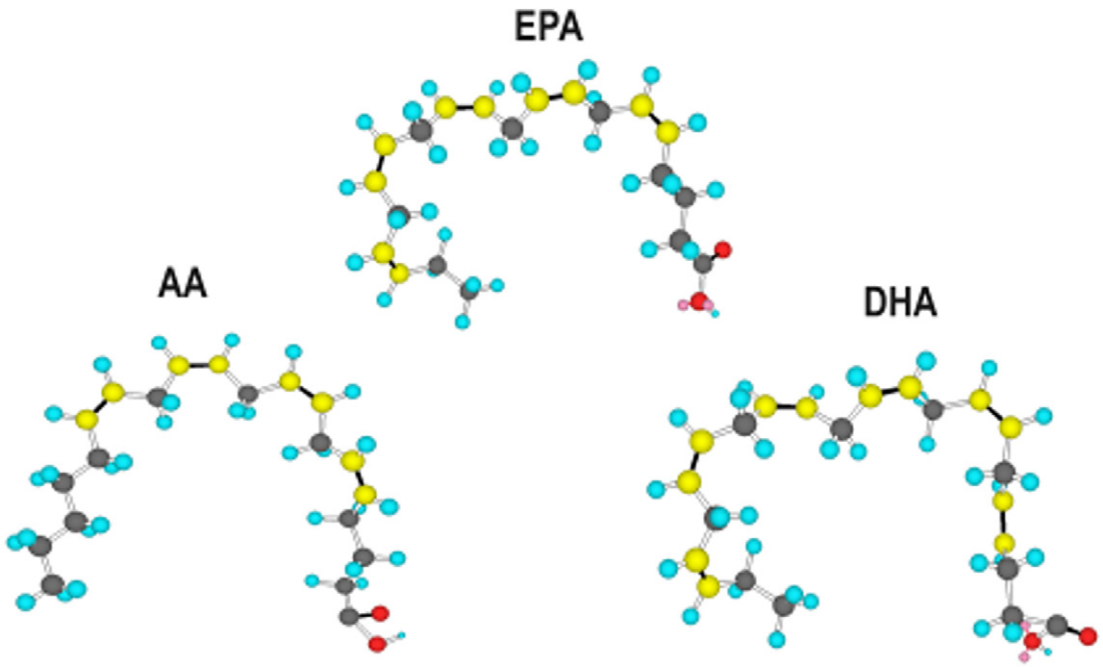

Fig. 2 – Ball and stick structures of AA, EPA, and DHA. Dietary and endogenous PUFAs serve as substrates for the biosynthesis of eCB as well as act as substrates for eicosanoids.

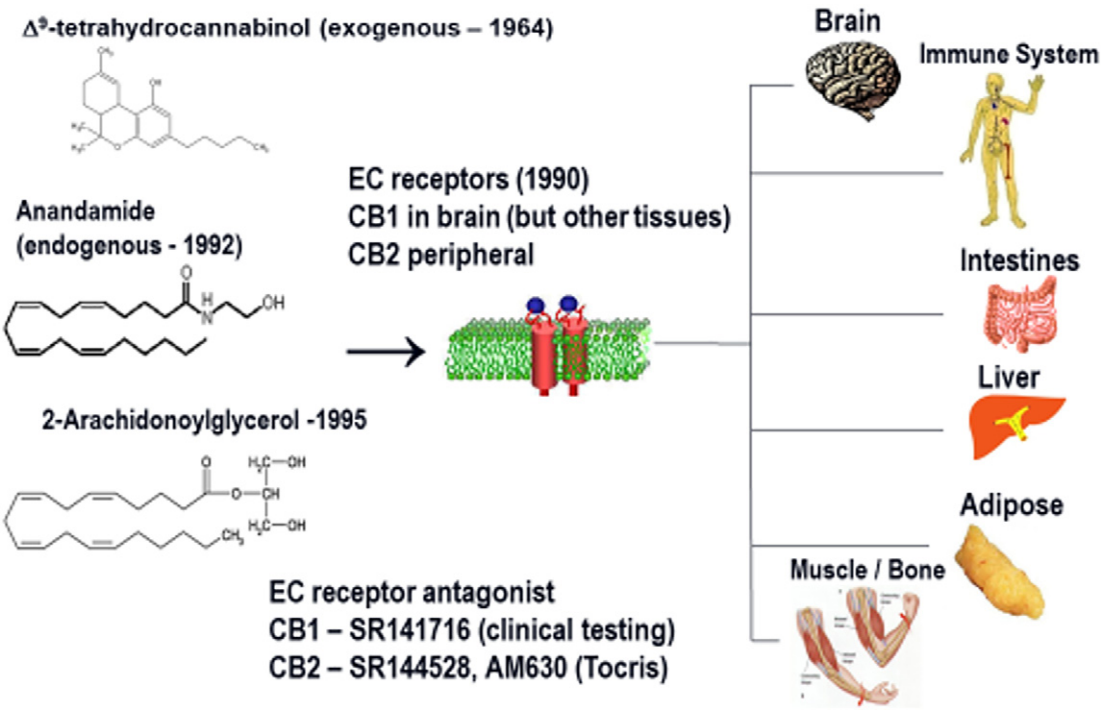

Fig. 3 – Endocannabinoid agonists and receptors actions. The eCB affect nutrient intake, metabolism, tissue accretion, and cell functions. The eCB AEA and 2-AG bind to both receptors CB1 and CB2. The AEA has higher affinity for CB1 compared to 2-AG. AEA and 2-AG are catalyzed by 2 different enzymes: N-arachidonoyl phosphatidylethanolamine phospholipase D for AEA and diacylglycerol lipase for 2-AG. Antagonists for the receptors reduce the binding of the agonists and, thus, signaling such as the suppression of appetite.

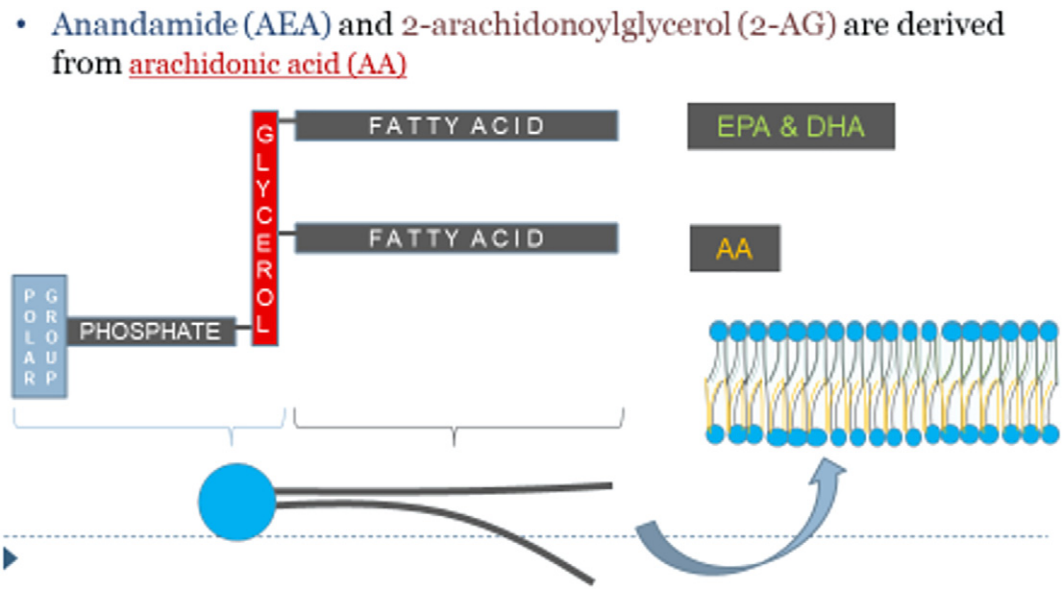

Fig. 4 – Dietary fatty acid remodeling of biomembrane lipids. The consequences on cell functions related to biochemistry and physiology to influence health and disease. Remodeling of biomembrane phospholipids by dietary or endogenously produced PUFAs. Changes in the amounts of arachidonic acid by increasing the n-3 PUFAs can reduce the agonist, AEA and 2-AG produced in cells and tissues.

AEA and 2-AG are fatty acid amide hydrolase, which acts on both AEA and 2-AG, and monoacylglycerol lipase, which is selective for 2-AG [26,27].

The AA-derived ligands of the ECS, AEA, and 2-AG influence many psychological and physiological functions, such as food intake and energy balance [28], pain perception [29], and memory processes [30]. Investigations on ECS regulation of systemic macronutrient energy balance show the relevancy of this system in obesity and diabetes. Recent reviews by our group [31] and others [32,33] summarized the actions of the ECS on systemic energy metabolism.

2.2. *Dietary PUFAs*

Remodeling the membrane phospholipid fatty acid composition with dietary PUFAs (Fig. 4) is one means to change the substrate for eCB formation, as well as redirect formation of eicosanoids or the collective group of oxylipin compounds (Fig. 5). Supplementing n-3 PUFAs in the form of EPA and DHA increases the concentrations of this family of PUFAs in membrane phospholipids (Fig. 4). Thus, with supplementation, the concentrations of *N*-docosahexaenoyl-ethanolamide are increased in mice [34] and postmenopausal women (Fig. 6) [35], which also altered the levels of some oxylipins. Therefore, it is reasonable that modification of membrane phospholipid fatty acid composition by dietary n-3 PUFA intervention can lead to changes in tissue production of eCB and oxylipins.

2.3. *ECS and metabolic activity and aging*

Studies support the concept that the ECS is in a state of overactivity, or altered tone, and the degree of stimulation of this system is due to the higher levels of ligands and thus dysregulated in human obesity. Therefore, understanding this overactivity and how it might be controlled can be translated to better health and aging in the adult. Butler and Korbonits used endocannabinoid tone in describing a state of overactivity related to obesity, and to reverse this excited state or overactivity would be explained as reduced endocannabinoid tone [36]. Furthermore, endocannabinoid tone or activity is a consequence of sensitivity of receptors to ligand binding and subsequent downstream responses from activation of the receptors; thus, elevated ligands such as AEA can promote higher activation [37].

Elevated levels of AA-derived endocannabinoids lead to increased tone implicated in obesity [38,39]. Upon activation of CB1, appetite is stimulated in the hypothalamus promoting lipogenesis, fat accretion, and impaired glucose uptake into skeletal muscle, thus resulting in an increase in body weight [1,40]. Recently, this could be reduced by the incorporation of n-3 PUFAs into the diet of mice which resulted in changing eCB levels and the subsequent actions on systemic metabolism in muscle and adipose [34]. The metabolic and physiologic changes associated with stimulation of the ECS are the reason for targeting the eCB signaling of receptors to control obesity and conditions of insulin resistance and diabetes [34].

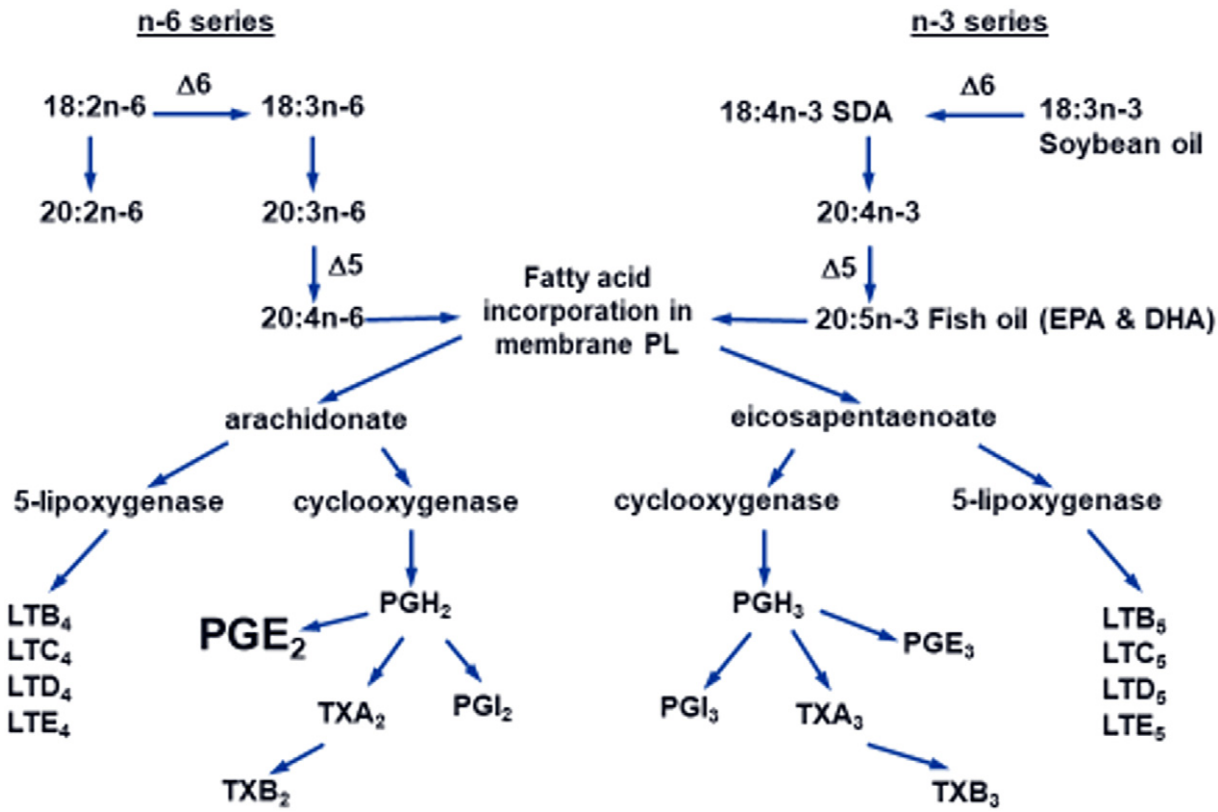

Fig. 5 – PUFA formation and biosynthesis of eicosanoids. Flux through the pathways is influenced by the dietary amounts of essential fatty acids (linoleic acid and linolenic acid) as well as the presence of stearidonic acid (18:4-n3) and the n-3 PUFAs EPA and DHA. An abundance of arachidonic acid relative to the n-3 PUFAs can lead to higher amounts of eicosanoids such as prostaglandin E_2 derived from AA. The eCB can serve as substrate for cyclooxygenase enzyme [49].

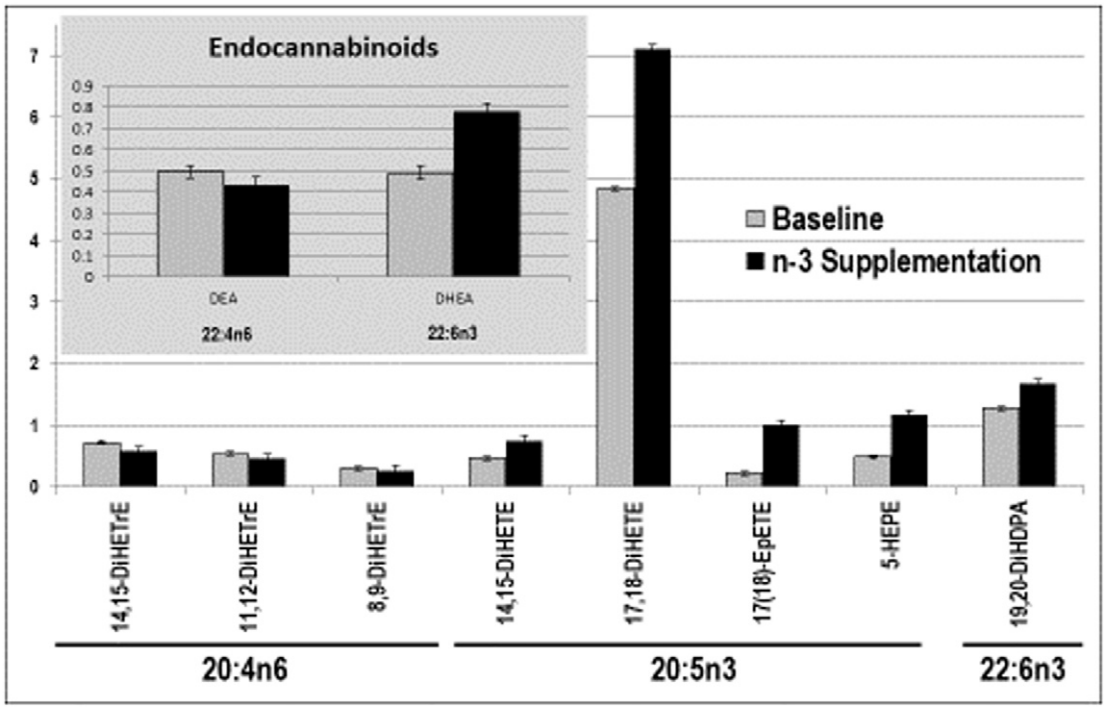

Fig. 6 – Serum levels of n-3 PUFA–derived eCB and oxylipins in postmenopausal women. After supplementation with n-3 PUFAs, levels of n-3–derived eCB and oxylipins were higher and n-6–derived lower in PMW after 6 months compared to baseline. Dietary n-3 PUFAs EPA and DHA can alter the concentrations of eCB and oxylipins in blood of mice [34] as observed in serum of postmenopausal women [35].

2.4. *A role for endocannabinoids in exercise*

The eCB mediate pathways of pain and act as analgesics in models of both acute nociception and clinical neuropathy [7]. The analgesic effects of eCB occur with binding to the cannabinoid receptors found in cells and tissues of the nervous system responsible for pain processing and in immune cells that regulate the neuroimmune interactions that convey the inflammatory signals [41]. Both cannabinoid receptors CB1 (in the central nervous system, localized in the plasma membrane) and CB2 (located in the peripheral tissues), in addition to enzymes for the synthesis and degradation of 2-AG, are part of the intricate signaling involved in pain processing for nociceptive and neuropathic pain [42]. Furthermore, beyond controlling pain, they aid in improvements for cognition and memory in adults that participate in moderate exercise [43,44].

An interesting aspect of the ECS is that exercise in the human was reported to increase the blood levels of AEA [45]. Post exercise of low and moderate intensity dramatically increases the blood levels of AEA in men and women [45]; however, the increase appears to be consistent for AEA, whereas in 1 study, no change was observed for 2-AG [46].

Physical activity is a recognized modifier of disease and the ECS, and the eCB appear to communicate the signals of physical activity in the brain [47]. Interestingly, exercise produces a positive well-being and may be responsible for what is commonly called the *runner's high* that is observed in some but not all runners [48]. Therefore, some findings suggest that this phenomenon of neurobiological reward might be associated with the ECS.

3. Conclusions

Diet is a primary lifestyle factor that influences the risk of chronic disease, whereas physical activity is another contributing aspect for maintaining health with aging. Interestingly, the ECS is emerging as a key component to control appetite, improve systemic metabolism, and reduce obesity and diabetes (Fig. 7). When considering dietary habits and exercise, the latter appears to affect both the types and levels of eCB and the functioning of the ECS. Moderate exercise is encouraged to maintain physical mobility and muscle strength and mass for the aging adult. Recent studies report an increase in the eCB AEA in blood after moderate aerobic exercise, and this increase in ligand seems to be positively associated with well-being. The ECS with its supporting enzymes and receptors is found in many organs and plays significant metabolic and physiologic roles. Moreover, the ECS is a functioning component in the central and peripheral nervous systems that is involved in pain and the neuroinflammatory pathways that are associated with pain. Dietary PUFAs, specifically n-6 and n-3 PUFAs, can alter the levels and types of substrate for the biosynthesis of eCB, and although the consequences are not fully known, diet in this example is another modifier of the ECS. In moving forward with nutrition research and health for adults, the ECS will be an intriguing effort of investigation to better understand the relationships of diet, appetite, and physical activity on obesity, diabetes, and pain (Fig. 7).

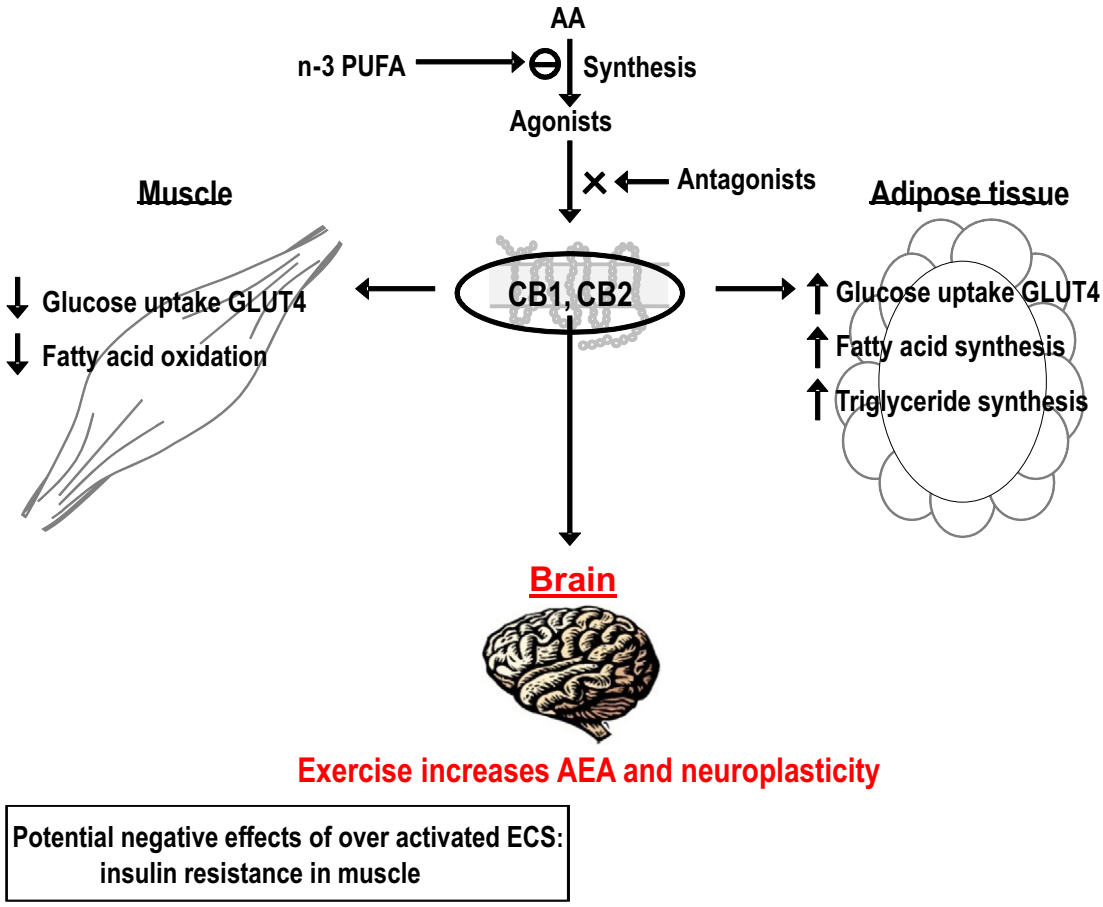

Fig. 7 – Overview of the ECS actions on muscle, adipose, and brain. Relationship between dietary PUFA, membrane phospholipids, and the synthesis of eCB. Formation of AA-derived eCB (such as AEA) and subsequent binding on the cannabinoid receptors CB1 and CB2 exert anabolic actions on muscle and adipose resulting in decreased use of macronutrients in muscle and generalized fat accretion in adipose. Supplying n-3 PUFAs in the diet decreases AA in membrane phospholipids and the anabolic effects downstream of ECS signaling. Overactivation of the ECS and high AEA can lead to obesity and reduced insulin sensitivity of muscle. Recent studies in rodents and humans reveal that AEA increases in brain and stimulates neuroplasticity (red fonts). The effects of n-3 PUFAs on the events of exercise on eCB in brain are not known. Antagonists of cannabinoid receptors were found to improve glucose uptake in muscle of mice and reduce fat accretion. Reduced fat accumulation is reported in humans given CB1 antagonists.

Acknowledgment

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