Dietary PUFAs and Exercise Dynamic Actions on Endocannabinoids in Brain: Consequences for Neural Plasticity and Neuroinflammation

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ABSTRACT

The brain and peripheral nervous system provide oversight to muscle physiology and metabolism. Muscle is the largest organ in the body and critical for glucose sensitivity, prevention of diabetes, and control of obesity. The central nervous system produces endocannabinoids (eCBs) that play a role in brain neurobiology, such as inflammation and pain. Interestingly, studies in humans and rodents show that a moderate duration of exercise increases eCBs in the brain and blood and influences cannabinoid receptors. Cannabinoid actions in the nervous system have advanced our understanding of pain, well-being, and disease. Nutrition is an important aspect of brain and eCB physiology because eCBs are biosynthesized from PUFAs. The primary eCB metabolites are derived from arachidonic acid, a 20:4n–6 (ω-6) PUFA, and the n–3 (ω-3) PUFAs, EPA and DHA. The eCBs bind to cannabinoid receptors CB1 and CB2 to exert a wide range of activities, such as stimulating appetite, influencing energy metabolism, supporting the immune system, and facilitating neuroplasticity. A diet containing different essential n–6 and n–3 PUFAs will dominate the formation of specific eCBs, and subsequently their actions as ligands for CB1 and CB2. The eCBs also function as substrates for cyclooxygenase enzymes, including potential substrates for the oxylipins (OxLs), which can be proinflammatory. Together, the eCBs and OxLs act as modulators of neuroinflammation. Thus, dietary PUFAs have implications for exercise responses via synthesis of eCBs and their effects on neuroinflammation. Neurotrophins also participate in interactions between diet and the eCBs, specifically brain-derived neurotrophic factor (BDNF). BDNF supports neuroplasticity in cooperation with the endocannabinoid system (ECS). This review will describe the role of PUFAs in eCB biosynthesis, discuss the ECS and OxLs in neuroinflammation, highlight the evidence for exercise effects on eCBs, and describe eCB and BDNF actions on neuroplasticity. *Adv Nutr* 2022;13:1989–2001.

Statement of Significance: This review describes the role that PUFAs play in eCB biosynthesis and eCB actions in the brain. Specifically the relations between PUFAs, eCBs, and OxLs in brain physiology and neuroinflammation and the impact of exercise on brain plasticity, pain, and well-being.

Introduction

The endocannabinoids (eCBs) exert multiple actions on systemic biology, macronutrient metabolism, the immune system, the brain, and the central and peripheral nervous systems. Investigations indicate that exercise induces the production of eCBs in the brain, and the eCBs participate in neurogenesis (1). In addition, the oxylipins (OxLs) are another group of lipid-derived bioactive lipids that influence the nervous system and contribute to neuroinflammation. In fact, the eCBs share with the OxLs some common features in substrates for their biosynthesis and metabolism (2). For example, both eCBs and OxLs are biosynthesized from similar n–6 (ω-6) and n–3 (ω-3) families of PUFAs.

Therefore, dietary lipids can be a fundamental factor that determines the types and amounts of eCBs and OxLs biosynthesized, and consequently, the effects of these bioactive lipids on cellular events, including those in the nervous system. The evidence for exercise elaboration of eCBs in the brain is revealing a better understanding of the benefits of exercise (3), from the young to the adult, especially as the interaction of physical activity and well-being are examined (4, 5).

The endocannabinoid system (ECS) consists of its endogenous ligand agonists, receptors CB1 (type 1) and CB2 (type 2), and enzymes for their biosynthesis and degradation. The eCBs are bioactive lipids including esters, amides, and
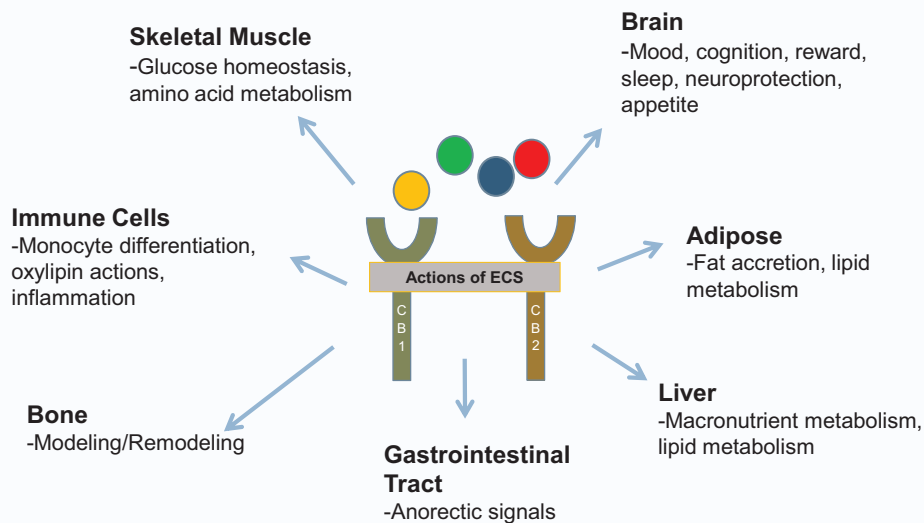
Figure 1 Systemic actions of the endocannabinoid system. Ligands for the ECS include those biosynthesized from arachidonic acid (20:4n–6), for example, anandamide (red) and 2-arachidonoylglycerol (orange), and those derived from DHA and EPA, N-docosahexaenoyl ethanolamide (green) and N-eicosapentaenoyl ethanolamide (blue). All endocannabinoid ligands bind to the receptors, CB1 and CB2, thus activating the ECS. The formation of oxylipins from cyclooxygenase enzymes and lipoxygenase enzymes utilizes substrates from the n–6 and n–3 PUFA families, as for the endocannabinoids. The oxylipins have numerous actions systemically and participate in several inflammatory responses. CB, cannabinoid receptor; ECS, endocannabinoid system.

ethers of arachidonic acid (AA; 20:4n–6), which mimic the effects of Δ^9-tetrahydrocannabinol (Δ^9-THC) as ligands activating CB1 and CB2 (6, 7). Although the eCBs have broad, diverse actions on many systems as shown in **Figure 1** (8), they support many functions in the brain and peripheral nervous system, especially with regards to neurobiology and neurophysiology, and have emerging roles in pain processing (antinociceptive and nociceptive mechanisms) (9).

N-arachidonoyl ethanolamide, or anandamide (AEA, which is an N-acylethanolamine), and 2-arachidonoylglycerol (2-AG) are the best known

eCBs. Intracellular membrane-associated phospholipases and lipases facilitate the synthesis/degradation of eCBs (**Figure 2**). Anandamide is biosynthesized from AA via NAPE-PLD (N-acylphosphatidyl ethanolamine–specific phospholipase D) and 2-AG by 2 enzymes, diacylglycerol lipase α (DAGLα) and diacylglycerol lipase β (DAGLβ). 2-AG and anandamide are inactivated by fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL), respectively. The endogenous production of AEA and 2-AG, and of N-docosahexaenoyl ethanolamide (DHEA) and N-eicosapentaenoyl ethanolamide (EPEA)—both products of DHA and EPA—is dependent upon tissue concentrations of n–6 and n–3 PUFAs, respectively. The amounts of n–3 PUFAs can shift the formation of n–3-derived eCBs (5) from AEA and 2-AG, and highlights the importance of understanding the effects of DHEA and EPEA. Furthermore, the biosynthesis of the OxLs via cyclooxygenase enzymes (COX1 and COX2) and lipoxygenase enzymes (LOX) uses similar families of PUFA substrates (**Figure 3**). The types of OxLs biosynthesized from the different PUFA families was described by Gabbs et al. (2) with attention to the specific actions of the OxLs. Therefore, dietary lipids (and to some extent endogenously synthesized long-chain PUFAs) can directly determine the metabolic and physiological outcomes of these compounds by changing the types of both eCBs and OxLs biosynthesized in cells and tissues.
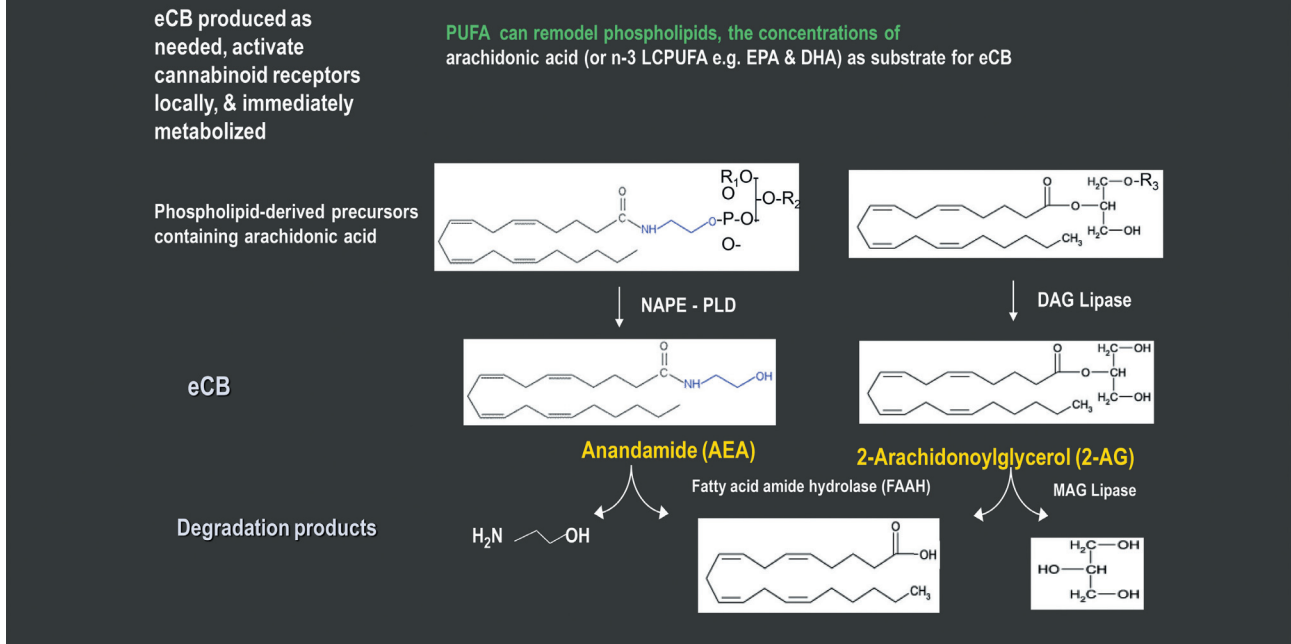
Figure 2 Synthesis and degradation of the endocannabinoids. The biosynthesis and degradation of eCBs derived from AA is accomplished by specific cellular lipase enzymes, as illustrated. Likewise, the eCBs DHEA and EPEA are produced by n–3 PUFAs (DHA and EPA) and share the same enzymes as shown for those metabolized from AA. The cellular/tissue balance between the n–6 and n–3 PUFAs determines the amounts and types of eCBs synthesized endogenously. AA, arachidonic acid (20:4n–6); AEA, anandamide; CB, cannabinoid receptor; DAG, diacylglycerol; DHEA, N-docosahexaenoyl ethanolamide; eCB, endocannabinoid; EPEA, N-eicosapentaenoyl ethanolamine; FAAH, fatty acid amide hydrolase; LCPUFA, long-chain polyunsaturated fatty acid; MAG, monoacylglycerol; NAPE-PLD, N-acylphosphatidyl ethanolamine–specific phospholipase D; 2-AG, 2-arachidonoylglycerol.

The purpose of this review is to describe the role that PUFAs play in eCB biosynthesis and eCB actions in the brain. The first objective is to present evidence for the relations between PUFAs, eCBs, and OxLs in brain physiology and neuroinflammation. The second objective is to describe the impact of exercise, which supports brain plasticity (10), with eCBs facilitating synaptic plasticity (5), and its consequences for pain and well-being.

Current Status of Knowledge

Dietary n–3 PUFAs, eCBs, and cannabinoid receptors in brain

As another group of eCBs, not metabolites of AA, those synthesized from long-chain n–3 PUFAs, both DHA and EPA, expedite synthesis of DHEA and EPEA, and both activate cannabinoid receptors but at lower potencies compared with AEA(11, 12). Kim et al. (13–15) observed that n–3 PUFAs can lower tissue AA concentrations and the synthesis of n–6 PUFA–derived eCBs. Likewise, DHA can lead to higher concentrations of DHEA in mice (15) and postmenopausal women, leading to a higher blood ratio of DHEA/AEA (16). In patients with depressive disorder, supplementation with

EPA led to higher EPEA concentrations relative to those of DHEA, whereas supplementation with EPA and DHA increased the concentration of DHEA more so than EPA treatment alone (17). In addition, our laboratory reported that feeding highly unsaturated n–3 PUFAs resulted in greater concentrations of n–3 PUFA–derived eCBs, and increased the abundance of mRNA for NAPE and DAGLα, and of CB1 and CB2 proteins in mouse muscle (18). Thus, studies show a distinct relation between dietary PUFAs and the type of eCBs produced and associated with the components of the ECS.

CB1 receptor expression is high in brain zones that largely affect aspects of feelings, memory, perception, movement coordination, and neural processing of pain. Because gene deletions for the CB1 receptor and FAAH enzyme suppress progenitor cells in the dentate gyrus (19–21), then logically the ECS is essential for nervous tissue growth and maturation. In contrast, operation of the immunocompetent system was first identified as a site of CB2 expression, followed by its discovery in peripheral nerves (22); CB2 is now recognized as part of the central nervous system (CNS) physiology (23). Importantly, the binding of eCB to the cannabinoid
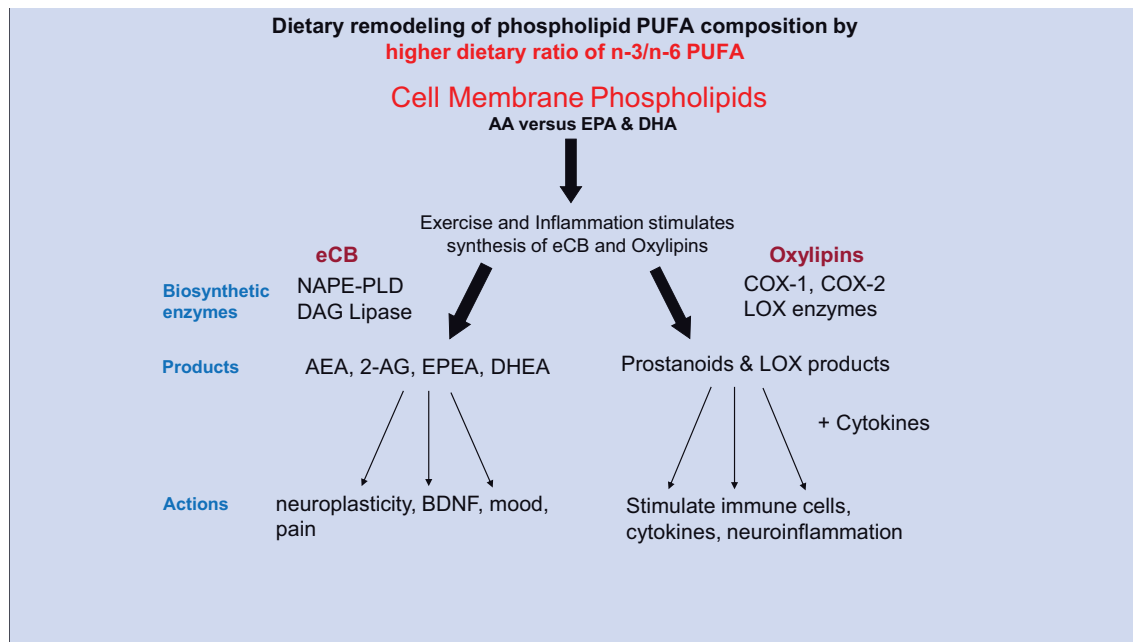
Figure 3 Relation between PUFAs and formation of endocannabinoids and oxylipins. Illustrated are the biochemical and physiological connections between dietary PUFAs and remodeling of the PUFA compositions in cellular phospholipids. The types of PUFAs in cellular membrane PLs determine what substrate is available for biosynthesis of eCBs and OxLs (via COX and LOX pathways). Both eCBs and OxLs have substrates in common, belonging to the families of long-chain n–6 and n–3 PUFAs. Hence, dietary PUFAs determine which eCBs and OxLs are elaborated, and the biological consequences of the specific actions of these different compounds are shown. Furthermore, this system is predominantly influenced by AA eCB agonists, because the Western diet is rich in n–6 PUFAs. However, a lower ratio of n–6/n–3 PUFAs, resulting from an elevated intake of EPA and DHA, reduces AA in tissue PLs, and thus lowers biosynthesis of AEA. Exercise increases AEA production in brain and blood; however, it is unknown if n–3 PUFA dietary supplementation replaces AEA while increases those derived from EPA and DHA in the nervous system. To date, it is unclear if EPEA and DHEA result in the same actions as AEA or cause more positive benefits from exercise. At present, the science suggests that reducing AA in tissue PLs with n–3 PUFAs lowers biosynthesis of proinflammatory OxLs and increases BDNF. AA, arachidonic acid (20:4n–6); AEA, anandamide; BDNF, brain-derived neurotrophic factor; COX, cyclooxygenase enzymes; DAG, diacylglycerol; DHEA, *N*-docosahexaenoyl ethanolamide; eCB, endocannabinoid; EPEA, *N*-eicosapentaenoyl ethanolamide; LOX, lipoxygenase enzymes; NAPE-PLD, *N*-acylphosphatidyl ethanolamine–specific phospholipase D; OxL, oxylipin; PL, phospholipid; 2-AG, arachidonoylglycerol.

receptors was reported to facilitate the neuroplasticity of synaptic processes (5, 24, 25).

The eCBs also bind to vanilloid receptor (transient receptor potential vanilloid, TRPV) and induce peripheral and central nervous system signaling pathways (26). Once eCBs bind, such as to the AEA-TRPV1 complex, the ligand receptor participates in nociception for the CNS (27) and other basic roles such as apoptosis (28, 29). Therefore, the science shows that the eCBs and their receptors are participants in the stimulation of nociceptors and, therefore, pain. Furthermore, both AA-derived eCBs are ligands for PPARA and PPARG (nuclear peroxisome proliferator-activated receptors), and binding thereto elevates carbohydrate and lipid metabolism (30) and supports inflammatory responses (31). Other eCB-like compounds, NAPE-PLD products, oleoylethanolamide (OEA) and palmitoylethanolamide (PEA), possibly act via triggering PPARA to influence appetite or modulate the immune system (31, 32).

Nutrition is an obvious approach to balance essential dietary PUFA families to re-establish eCB dysfunction or reduce an upregulated ECS found in pathophysiological conditions. Diet is less invasive and has minimal side effects compared with a pharmacological treatment to restore eCB tone. Further, it was hypothesized that ECS hypofunction is a possible clinical outcome where reversal of low eCB concentrations may decrease pain and result in better sleep (33). Therefore, diet is a reasonable means to achieve a balance and restore eCB tone using an optimum ratio of n–6/n–3 dietary PUFAs for eCB substrates and the desired outcome (12, 13).

n–3 PUFAs and brain-derived neurotrophic factor in brain.

Studies of per capita fish and seafood consumption, a proposed measure of dietary intake of EPA and DHA together (i.e., fish oil), indicate that low consumption of these food sources is accompanied by a greater occurrence of bipolar disorders and depression (34, 35). Interestingly, n–3 PUFAs have a modulatory effect on brain-derived neurotrophic factor (BDNF) (36), a factor supporting brain neuroplasticity

Moderate exercise increases the eCB in brain and blood

↓

Dietary n-3 PUFAs

Brain

Blood

n-3 PUFAs, EPA and DHA, lower arachidonate and potentially reduce AEA and 2-AG production

↑ eCB DHEA & ↑ BDNF in brain supporting neuroplasticity

Increases less inflammatory and lowers pro-inflammatory oxylipins in brain/blood

Receptors
CB1 CB2

Elevated levels of eCBs & systemic actions on macronutrient metabolism – Target organs: Systemic actions on muscle, liver, & adipose

AEA increases pro-inflammatory oxylipins in contrast n-3 PUFAs lower inflammatory oxylipins and cytokine production

Exercise increases AEA and neuroplasticity. The n-3 PUFAs via eCB (DHEA) appears to rescue BDNF levels. Brain and peripheral nervous system effects appear to influence well-being and reduce inflammation and pain.

Figure 4 Dietary DHA and EPA and exercise increase BDNF expression, playing a role in brain physiology, neurogenesis, and plasticity. The synthesis of eCBs and OxLs shares substrates from both n–6 and n–3 families of PUFAs. Therefore, PUFAs determine the types of eCBs and OxLs biosynthesized and ultimately result in potentially different physiological actions (e.g., proinflammatory or less proinflammatory). The ECS is mainly mediated by AA eCB agonists; however, EPA may lower AA eCB agonists in brain and other organs and tissues. Supplementing dietary n–3 PUFAs will reduce the cellular phospholipid content of AA (see Figure 3) and lower biosynthesis of AEA. During moderate physical activity, when AEA is increased, it is not clear if n–3 PUFAs can replace AEA with EPEA or DHEA in brain. It is unknown if the eCBs EPEA and DHEA mediate the same effects as AEA or have different actions during exercise. Currently, replacement of AA in phospholipids with n–3 PUFAs is thought to reduce the production of proinflammatory OxLs and likely improve BDNF levels. AA, arachidonic acid (20:4n–6); AEA, anandamide; BDNF, brain-derived neurotrophic factor; CB1 and CB2, cannabinoid receptors; DHEA, *N*-docosahexaenoyl ethanolamide; eCB, endocannabinoid; ECS, endocannabinoid system; EPEA, *N*-eicosapentaenoyl ethanolamide; OxL, oxylipin; 2-AG, arachidonoylglycerol.

and neurogenesis (37, 38) and learning processes. For instance, dietary n–3 PUFAs showed a positive relation with BDNF serum concentration in adolescents, suggesting an association between BDNF and mental disorders linked to n–3 PUFAs (39). Moreover, during pregnancy and lactation, n–3 PUFA deficiency will have a permanent, detrimental effect on adult progeny neurogenesis; thus, the findings imply that the harmful outcomes of deficiency might be attributable to the interplay of environment and expression on BDNF (40).

Sources of dietary DHA cause a concomitant decrease in tissue AA such that both higher DHA and protein expression of BDNF are positively correlated in brain (41, 42). In addition, even though DHA in brain is found at a greater concentration than EPA, findings show that EPA has greater biological activity in the brain on BDNF than DHA and benefits for mental and behavioral conditions (43) and depression (44). In *FAT1* mice, sources of long-chain n–3 PUFAs reduced depression-like behavior and supported anti-inflammatory conditions by attenuating amounts of proinflammatory cytokines and enhancing anti-inflammatory cytokines (45).

DHA with exercise improved BDNF expression and cognition associated with synaptic plasticity compared with either DHA or exercise alone. The research in rats indicates synergism of n–3 PUFAs and exercise (**Figure 4**) to benefit neural plasticity (8). Therefore, DHA and EPA affect cellular processes related to behavioral disorders by changing the PUFA composition of cellular lipids in specific regions of the brain, leading to effects on social aspects (e.g., behavior) and improved neurodevelopment (46).

OxLs and inflammation in the brain

Illustrated in Figure 3 are the types of OxLs derived from the n–6 and n–3 PUFAs and the enzymatic routes for their biosynthesis. The OxLs participate in brain neuroinflammatory processes and the peripheral nervous system to impact inflammatory pain processes. Phospholipase A_2 activated during inflammatory processes (47) releases PUFAs for OxL biosynthesis. Generally, 3 pathways contribute to the formation of OxLs: *1*) COX and by synthases, *2*) LOX, and *3*) cytochrome P450 (CYP) and other oxidase enzymes (47). These 3 pathways result in the formation of the typical products synthesized from 20-carbon PUFAs, which are

eicosanoids derived from AA and EPA; however, DHA leads to products called docosanoids. Collectively, these products have been called OxLs and are produced as an alternative fate of the eCBs (48). Changing the proportional distribution of PUFA families or the ratio of n–6/n–3 PUFAs ultimately alters the substrates for COX and LOX enzymes.

The specialized n–3 PUFA OxL products are resolvins (Rv), protectins, and maresins, which end inflammation, whereas those from AA share in the physiological processes of pain (49), which includes neuroplasticity (50). DHA products are D-series resolvins (RvDs), protectins, and maresins, whereas those from EPA are the E-series resolvins (51); these products are recognized for their anti-inflammatory/proresolving activity (52). Resolvins (D1, E1, D2, and other related compounds) also reduced pain caused by inflammation and chronic pain in an animal model (53). Another group of n–3 PUFAs, LOX metabolites, include electrophilic fatty acid oxo-derivatives (EFOX), 7-oxo-DHA, 7-oxo-docosapentaenoic acid (DPA; 22:5n–3), and 5-oxo-EPA, metabolites from DHA, DPA, and EPA, respectively (54). EFOXs demonstrate many anti-inflammatory properties, such as acting as agonists for nuclear PPARs as well as inhibiting cytokine elaboration in macrophages (55). In support of actions from n–3 PUFAs, healthy subjects given n–3 PUFAs showed elevated formation of 7-oxo-DHA and 5-oxo-EPA in immunocompetent cells (54). In addition, the CYP epoxygenases and -hydrolases result in metabolites of AA including regio- and stereoisomers of epoxy-eicosatetraenoic acids (56) and hydroxyeicosatetraenoate (HETE); metabolites of EPA including epoxy-eicosatetraenoic acids, HEPE (hydroxy-eicosapentaenoic acids), and epoxydocosapentaenoic acids; and DHA hydroxide (57). The isoforms of CYP selectively use EPA, and the metabolites of AA and DHA occur at the same frequency (57).

With respect to dietary modification of OxL synthesis, postmenopausal women given a supplement of n–3 PUFAs had higher OxL metabolites of n–3 PUFAs [14,15-hydroxyeicosatetraenoic acid (DiHETE), 17,18-DiHETE, 17(18)-epoxyeicosatetraenoic acid (EpETE), 5-HEPE, and 19,20-dihydroxydocosapentaenoic acid (DiHDoPE)] but lower n–6 metabolites [14,15-hydroxyeicosatetraenoic acid (cytochrome P450 eicosanoids, DiHETrE), 11,12-DiHETrE, and 8,9-DiHETrE] in blood compared with the placebo oil (16). In these women, DHA supplementation reduced inflammatory OxLs but also increased blood concentrations of DHEA, the eCB metabolite of DHA that improves eCB tone (16). DHEA and OxLs synthesized from DHA support greater anti-inflammatory activity than AA OxL metabolites (58). In transgenic mice used as a model to understand the effects of varying the endogenous ratio of n–6/n–3 PUFAs on disease risk, the *FAT2* transgenic mice (which synthesize more n–6 PUFAs compared with *FAT1* mice, which synthesize n–3 PUFAs from n–6 PUFAs) showed higher serum concentrations of cytokines (TNFα, IL-6, and IL-1β) and OxL (12-HETE) compared with the inflammatory marker concentrations in wild-type and *FAT1* mice (59). Increased tissue n–6 PUFA content and an elevated

ratio of n–6/n–3 PUFAs can generate a serum metabolite profile (inflammatory OxLs) that encourages a physiological environment for metabolic disorders and loss of eCB tone with regard to forms and amounts of eCBs.

Features of eCBs and OxLs during exercise

Exercise induces neural plasticity (5) and brain functional connectivity (60), and increases eCBs in the brain (12). The eCBs influence neuronal plasticity (5) and several responses that support the positive actions of exercise on the brain (10) and likely act as agents to improve emotional state (61). CB1 colocalizes with type-2 dopamine receptors (62), enhances AEA production (63), and appears to support the premise that eCB control of voluntary movement occurs with the support of dopamine receptors within the basal nuclei for motor control. The eCB and exercise connection is an intriguing avenue of CNS investigation where dietary PUFAs play a dynamic role in pain, well-being, and neuroplasticity (1, 4). Greater hippocampal neurogenesis is matched by higher concentrations of AEA and increased CB1 activity, and such changes are positively linked to BDNF activity (24, 64). BDNF is a positive factor for brain emotion, and lowered brain BDNF concentration markedly induces anxiety and contributes to depression but is reversed with voluntary running in a rodent model (65). During exercise, the observed rise in blood eCB can cause lowered perception of pain. For instance, in women PEA and *N*-stearoyl ethanolamide eCB congener concentrations were observed to be associated with reduced chronic pain intensity after low-impact exercise (66). In support of these findings, antagonists of CB1 and CB2 injected into subjects resulted in pain-relieving outcomes similar to those from exercise.

Physical activity increases catabolism, metabolic activity, and changes in the hypothalamus (abundance of CB1) to induce eating and reverse the waning of energy stores (67). Energy expenditure can specifically activate appetite induced by AEA. Exercise and eCBs in the rat increase the concentration of orexigenic neuropeptide Y (68) via release in the hypothalamus (69), which increases rodent feeding behavior (70). In support of these findings, CB1$^{-/-}$ mice, like the FAAH$^{-/-}$ mice, are slim and exhibit low food intake (71, 72); however, mice given to running wheel exercise had induced CB1 inverse agonist–dependent reduction of appetite (73). Thus, these results show that eCB effects on feeding require CB1. Moreover, exercise is a positive factor for systemic energy homeostasis, whereas eCB derived from n–6 PUFAs generally has an opposite action (4).

Short-term exercise increases OxLs, which, to an extent, affect transient immune and physiological responses (74). The change in OxL concentrations observed following exercise is another link between eCBs and inflammation, and data from the aforementioned study suggests that aggressive aerobic exercise increases a plethora of plasma OxLs generated from various PUFAs. Concentrations of OxLs synthesized from AA included many HETEs and DiHETrEs in plasma as found postexercise, and the investigators suggest the changes are found with inflammation and oxidative stress

(75). Furthermore, injections of CB1 and CB2 antagonists and transport and hydrolysis inhibitors of eCBs suggest that eCB congeners provide analgesic outcomes from exercise (76). Therefore, it is evident that OxLs and eCBs are vital factors in the physiological outcomes of exercise and in neuroinflammation (Figure 4), with the provision that the types and amounts of eCBs and OxLs are determined by dietary PUFAs (Figure 2).

Neuroinflammation, eCBs, and OxLs

Neuroinflammation is a region-specific condition in the CNS and peripheral nerves, which facilitates restoration of damaged neural cells and associated neuroglia; but excess neuroinflammation can stall neuron renewal (77). Uncontrolled neuroinflammation can contribute to CNS disorders such as neurological and neuropsychiatric diseases. The ECS, when upregulated during neuroinflammation, can afford anti-inflammatory effects (78). The eCBs are secreted via microglial extracellular membrane vesicles in the brain, and these vesicles carry AEA to cell surfaces to stimulate neuronal CB1 and block transmission to synapse. CB1 is the primary receptor for eCBs in brain (62) and is likely the primary player for neuroinflammatory disease states of the CNS, such as demyelinating diseases (79). Neuropathic pain is mediated in the spinal cord and brain, where it is found with release of proinflammatory cytokines (ILs and TNFα) (80).

Generally, the Western diet is high in n–6 PUFAs, relative to the small amounts of n–3 PUFAs. Herein, the discussion now focuses on dietary intake of n–3 PUFAs, which change concentrations of eCBs, AEA, EPEA, and DHEA, but also the concentration of proinflammatory and anti-inflammatory OxLs (12, 81, 82). In support of these dietary lipid relations, both EPEA and DHEA in peritoneal macrophages from mice given n–3 PUFAs reduced LPS-induced elaboration of proinflammatory chemokines (83). Furthermore, postmenopausal women given n–3 PUFAs showed greater amounts of OxLs synthesized from EPA and lower amounts from AA metabolites compared with the placebo group (16), validating that dietary PUFAs change the types of OxLs elaborated in humans.

Kim et al. (15) reported decreases in the 5-lipoxygenase pathway proinflammatory OxLs in mice fed a DHA-supplemented semipurified diet compared with controls, indicating a lower inflammatory state. That n–3 PUFAs direct production of specific prostanoids via the COX enzymes and change the concentrations of inflammatory mediators is well known; however, it has been shown that COX enzymes can utilize eCBs (84). Changes in concentrations of eCBs, accompanied by lower concentrations of inflammatory mediators like OxLs and cytokines are likely in part a result of alterations in inflammatory pain and benefit mood following exercise. At this time, how extensively EPEA and DHEA are biosynthesized from n–3 PUFAs and alter eCB signaling or brain physiology is unknown (1). Some neuroinflammation is vital for normal CNS physiology, whereas high levels are damaging to the CNS. Exercise increases AEA in blood and brain; further, both eCBs and OxLs are key players in neuroinflammation and plasticity. PUFA type, and likely concentration, such as n–3 PUFAs in the diet, appear to decrease inflammatory OxLs in the CNS (Figure 4).

Exercise and eCBs: evidence from human and animal studies

Currently, 12 human investigations indicate that exercise increases blood concentrations of eCBs. These studies demonstrated amplification of AEA in plasma after exercise (85–90), and in most cases, 2-AG remained unchanged (85, 86, 88–91). These studies also showed that 2 congeners of AEA (OEA and PEA) experienced changes like AEA (85, 88, 91).

In another study, exercise effects on concentrations of eCB in plasma in humans were contrasted with effects in the dog (a cursorial mammal) and ferret (a noncursorial species) (90). These investigators reported that humans are similar to dogs for exercise-induced physiologically increased blood AEA, but both lacked any difference in 2-AG following 30 min of high-intensity running. Neither human nor dog showed eCB changes following 30 min of walking, a less intense exercise (90). Higher concentrations of AEA following exercise were observed centrally in rodents (92–95). Like the findings in humans, in rats plasma 2-AG did not change after exercise (96, 97). Hill et al. (24, 98) found that running wheels led to higher total AEA but not 2-AG in the hippocampus, and no difference in maximal FAAH activity, and thus a likely increase in synthesis of AEA during exercise. Although exercise in rodents is not the same as voluntary exercise in humans, the findings for AEA in rodents seem to be consistent with humans. Unlike the finding in humans that exercise does not affect 2-AG, treadmill exercise to fatigue (94) and restraint stress (25) both led to higher AEA and 2-AG in mice.

In mice, exercise induced AEA biosynthesis after 8 wk of consistent running but there were no differences in hepatic expression of FAAH, CB1, and CB2 (99). Swenson (100) reported that exercise in female and male mice did not alter receptor expression for CB1. Interestingly, caloric restriction combined with consistent exercise in human subjects decreased abdominal fat expression of the FAAH gene, which might suggest reduced food intake prevents AEA degradation (101). It should be noted that FAAH degrades AEA, OEA, and PEA but MAGL degrades 2-AG, supporting a common pattern of changes following exercise, with only 2-AG concentrations different due to MAGL enzyme control.

In another experiment, acute aerobic exercise in rats caused increased plasma concentrations of AEA, OEA, PEA, and 2-AG; furthermore, exercise also resulted in cannabinoid receptor (CB1 and CB2) effects on pathways in blocking detection of pain (94). These observations corroborate some previous reports of exercise-induced elevation of eCBs but must be examined to ascertain if the exercise increase in eCBs occurs via a genomic mechanism and to confirm effects on antinociception pain signals (peripheral and CNS) or well-being.

During exercise intensity, AEA changes are likely dependent on physiological response but indirectly supported, thus lacking in the full implications. For example, AEA plasma concentrations were elevated after 30–45 min of moderate physical activity involving running and cycling; however, this was not observed with low- or high-vigor exercise based on peak heart rate of 44% and 92%, respectively (86, 88–90). Human subjects were assigned to periods of moderate, long-duration exercise of hiking in a normoxic environment (4–4.5 h) or in a hypoxic environment (3.5–5.5 h), and the subjects showed a 2- and 3-fold increase in blood AEA, respectively; however, no change in 2-AG was observed (89). In a study of fasted, postmenopausal women, cycling but not dancing caused a rise in plasma OEA (91). Logically, the key to these findings is understanding the reason for the physiological increase of AEA during specific intensities of exercise, that is, what is the mechanism and relation between the brain and muscle?

Thompson et al. (92) reported higher AEA and lower 2-AG expressed in female compared with baseline male mice; but following wheel exercise, AEA was higher in both sexes relative to control mice. However, the concentration of 2-AG decreased with wheel exercise in females but did the opposite in male control mice. The sex disparities are not surprising; for example, differences in sex were noted for the responses in these mice when subjected to wheel running and CB1 agonists and antagonists (102, 103). On a different aspect of the ECS–gender interaction, receptor CB1 expression was similar for both sexes of mice after exercise, but at baseline female mice had lower amounts of CB1 than male mice (100). Interestingly, adolescent girls are more susceptible to problems with CB1 signaling with repeated use of Δ^9-THC compared with males of equivalent age (104), and females are more responsive to cannabis compared with males (105).

At this time, no evidence from exercise studies indicates differences in CB1 between females and males at baseline or for basal concentrations of AA-derived eCBs or EPEA and DHEA. No study has examined the effects of exercise regimens on eCBs in subjects of different ages; however, experiments in rodents suggest that eCBs and perhaps the receptors for eCBs are subject to deficits associated with aging (106). As an example, old mice have lower concentrations of AA-derived eCBs in brain when compared with younger rodents (107, 108). Furthermore, with increasing age, the CB1 receptors decline as well as the enzymes NAPE-PLD and DAGL (106). Interestingly, it is recognized that in aging mice, lowered DAGL but higher MAGL results in declining eCBs such as hippocampal 2-AG (108).

Currently, insufficient evidence is available for the human to ascertain how exercise affects all levels of eCBs and the degree of ECS participation in exercise for different sexes. Such an understanding of these critical physiological processes will likely benefit studies of aging and pain in humans. The potential benefits of dietary PUFAs as substrates for eCBs will be a strategic aim of new research on the relations between the brain and ECS, as shown in Figure 4.

The role for eCBs and BDNF in neuroplasticity and neurogenesis

Neuroplasticity of the CNS is affected by intrinsic/extrinsic stimuli to induce reorganization of the structure, function, and connectivity of the CNS (109). The eCBs contribute to neuroplasticity, both short term and long term, in the formation of new neural synaptic connections with the participation of cannabinoid receptors (5). Neurotrophins (i.e., BDNF) are necessary players in neuroplasticity, supporting neurogenesis, as shown in **Figure 5** (38). The neurotrophic actions of BDNF induce the transcription factor cAMP response element binding protein (CREBP). Once CREBP is activated, genes are expressed for the survival of neural cells and to support the capacity for neural plasticity. Irregularities in neurotrophin brain expression elicit changes precipitating neuropathological conditions. It was reported that in $BDNF^{+/-}$ mice, neurotrophin was necessary for potentiating alterations in synaptic potency (110), and infusion of this neurotrophin promoted long-term potentiation (LTP) and elicited synaptic strengthening in rat hippocampus (111, 112). Furthermore, in subjects having a despondent state compared with patients in recovery, structural MRI analysis revealed reduced LTP and BDNF expression (113). These observations support the premise that BDNF participates in the control of neuroplasticity, likely by affecting neurogenesis and synaptic plasticity.

The chief active component of cannabis, Δ^9-THC, promotes upregulation of BDNF expression (64), so in effect BDNF restores the loss of mental attributes caused by Δ^9-THC use (114). Clinical studies in humans also suggest that intermittent use of Δ^9-THC changes the concentration of BDNF in blood (115). Furthermore, cannabinoids were observed to induce CREBP phosphorylation (116) and change BDNF and CREBP expression (117). No human study has reported a direct effect of n–3 PUFAs on neurotrophins, except via the eCB DHEA, which increased BDNF by influencing neural stem cell differentiation through participation of protein kinase A and CREBP (118, 119). Clearly, more research is needed to discern the roles of DHA and DHEA on BDNF.

Exercise is beneficial for neuroplasticity (Figure 5). As an example, data from various studies revealed the outcome of acute aerobic exercise and elevated basal peripheral BDNF concentrations; however, the effect was temporary (120). Furthermore, swimming by stressed rodents resulted in antidepressant-like effects on hedonia and was followed with a stabilizing of lowered expression of BDNF mRNA (121). Exercise increases anandamide (perhaps not 2-AG) and BDNF that are positively correlated, and at the termination of moderate physical intensity following a 15-min rest. In this regard, in young male cyclists it was shown that the AEA increment during cycling likely supports increases in peripheral BDNF concentrations, and that elevated AEA
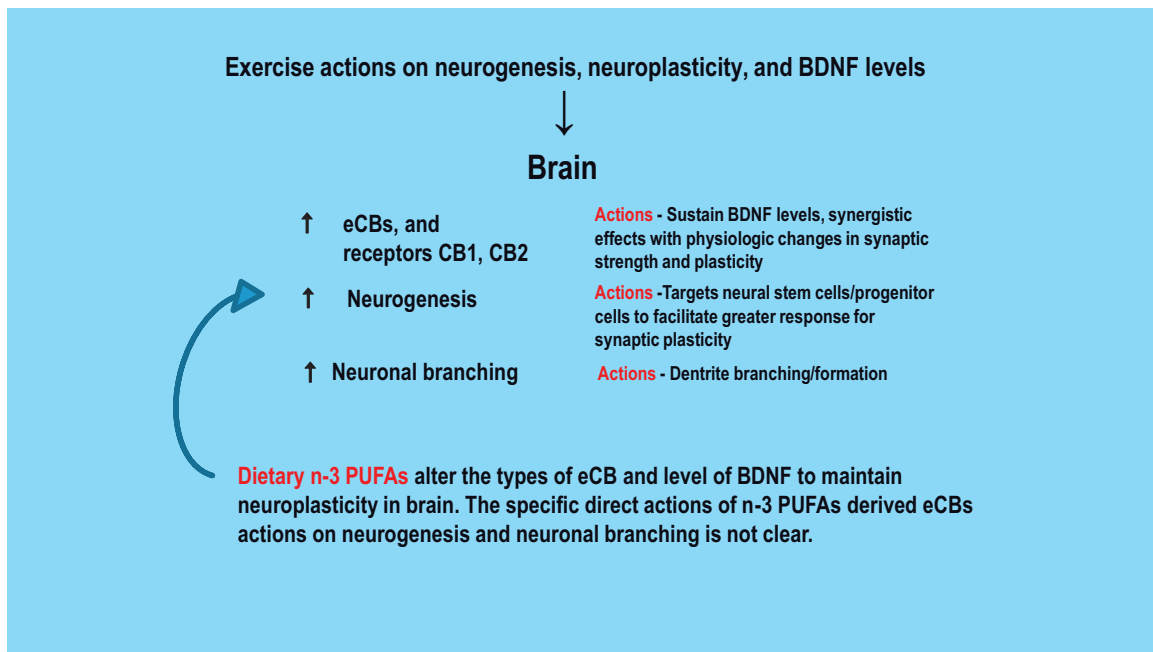
Figure 5 Exercise actions on neurogenesis, neuroplasticity, and BDNF concentrations. Exercise imparts effects on the brain that are vital for neurogenesis and neuroplasticity. The capacity to influence neurobiological events, such as thought processes and adaptive changes for control of movement throughout life, depends on eCBs and OxLs. BDNF concentrations are increased by exercise and complement neuroplasticity. As explained, eCBs participate in how exercise influences the central nervous system, and the cannabinoid CB2 receptor has a preeminent role in altering the amount of BDNF in the brain. In addition, moderate physical activity increases OxLs and as a consequence alters downstream factors to impact processes of inflammatory pain. BDNF, brain-derived neurotrophic factor; CB1 and CB2, cannabinoid receptors; eCB, endocannabinoid; OxL, oxylipin.

concentrations while in recovery sustain BDNF concentration after exercise, preventing a rapid return to basal concentrations ([88]). Therefore, investigations on exercise and eCBs should include neurotrophins, which likely influence their actions on neuroplasticity ([88]). The exercise-induced increase of BDNF enhances favorable physiological processes in the brain, such as neuroplasticity and connectivity, which improve cognition and well-being ([122], [123]).

It is intriguing to integrate the evidence for n–3 PUFA actions on increasing BDNF concentrations given that the existing recognized health aspects of n–3 PUFAs in the brain might be connected to BDNF for improving mood and behavior. However, the benefits of n–3 PUFAs in consideration of eCBs have not been investigated in the human. In particular, nerve growth factor (NGF) was found to participate in neuroplasticity and other aspects of neuronal physiology ([124], [125]). The actions of neurotrophins and research on dietary EPA and DHA showing effects on gene-level regulation of NGF and CREBP, suggest that both n–3 PUFAs and neurotrophins (such as NGF) are important in preventing disorders of the CNS ([41]). Accordingly, more evidence is needed to better determine the role of EPA and DHA in CNS physiology, and of neurotrophins associated with the processes of neurogenesis and neuroplasticity, in which eCBs participate and affect BDNF expression.

Conclusions

One outcome of moderate exercise is the elevation in concentrations of AEA in brain and blood. In addition, intensive aerobic exercise of long duration causes an increase of plasma OxLs biosynthesized from PUFA substrates through the actions of COX and LOX enzymes and cytochrome enzymes. Thus, a major nutrition and health research effort is needed to better understand neuroinflammation and the control of inflammatory pain mechanisms. The synergism between physical activity and the actions of DHA and DHEA to increase expression of neurotrophins and synaptic plasticity is another reason to study exercise, n–3 PUFAs, and the brain. These relations reveal important complementary actions of EPA and DHA with physical activity to support brain health. The actions of n–3 PUFAs in specific brain areas important to well-being and pain are emerging with the advancing knowledge of eCBs and OxLs. Moreover, the eCBs and their congeners support the analgesic outcomes of exercise, either centrally or peripherally.

Although we have good evidence that eCBs and OxLs are produced and contribute to the physiology of the brain and the peripheral nervous system, many specifics of their mechanisms in brain health are unknown. New research must explore the relations between dietary PUFAs, endogenous eCB precursors, and exercise and their role in pain. Unfortunately, at present, how exercise and dietary n–3

PUFAs influence the milieu of eCBs and OxLs in the CNS is not quantified or described.

How eCBs and the ECS operate in exercise must be elucidated, giving careful attention to sex, aging, and dietary PUFA type and concentration. The incomplete metabolomic analysis for all eCBs in blood at rest and various conditions of physical activity is delaying progress in understanding their function in health. Moreover, a mind and body exercise like Tai Chi and its effects on eCBs and OxLs should be studied. Future efforts must be directed to developing animal models to identify mechanisms of how eCBs and OxLs impact neuroinflammation. Investigations that explicate how eCBs and OxLs influence the actions of neurotrophins in the CNS will complement the research. In these endeavors it will be helpful to identify specific biomarkers that participate with the eCBs and OxLs during exercise to benefit aging.

Acknowledgments

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