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Chapter 6

Dietary Omega-6/Omega-3 and Endocannabinoids: Implications for Brain Health and Diseases

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Additional information is available at the end of the chapter

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Abstract

Omega-3 (ω-3) and omega-6 (ω-6) are polyunsaturated fatty acids (PUFAs) that play critical role in human health and have to be provided by food. In the brain, PUFAs are also precursors of endocannabinoids. The aim of this chapter is to review the existing literature on how dietary PUFAs impact on the endocannabinoid system in the brain and what are the consequences for brain function and dysfunction. In this chapter, we will first describe how PUFAs enter the brain, what are their metabolism processes and roles in brain function. We will describe the pathways from PUFAs to endocannabinoid production. Then, we will review the literature on how dietary ω-6/ω-3 ratio impacts the endocannabinoid system, in terms of endocannabinoid levels, proteins and endocannabinoid-dependent synaptic plasticity. In the next part, we will describe what we know about the interactions between PUFAs and endocannabinoids in neurological and neuropsychiatric disorders. Finally, we will conclude on the possible implications of the interactions between dietary PUFAs and endocannabinoids in the normal and pathological brain. In particular, we will discuss how dietary PUFAs, as homeostatic regulators of endocannabinoids, can constitute interesting therapeutic strategies for the prevention and/or treatment of neurological disorders with endocannabinoids impairment.

Keywords: brain, polyunsaturated fatty acids, endocannabinoids, omega-3, synaptic plasticity

1. Introduction

Polyunsaturated fatty acids (PUFAs) are essential constituents of plasma membranes and depending on their chemical structure, PUFAs are of the n-3 or the n-6 family and are common-

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ly called ω-3 or ω-6, respectively. In addition, PUFAs are precursors of an almost infinite variety of metabolites, and endocannabinoids are part of them. In particular, anandamide and 2-arachidonoylglycerol (2-AG), the two major endocannabinoids in the brain, are directly derived from arachidonic acid (ARA), the more abundant ω-6 PUFA in the brain. Interestingly, other endocannabinoids are derived from ω-3 PUFA, but their role in the brain remains elusive.

Amount of ω-3 and ω-6 PUFAs provided by food has direct consequences on their bioavailability and it has been established that the ideal ratio in the diet is of about 5:1 of ω-6:ω-3 PUFAs precursors. However, our modern diet is hugely unbalanced with an estimated average ratio of 20:1 [1]. The dietary deficit in ω-3 PUFAs has been associated with numerous diseases, and it becomes evident that imbalance of ω-3/ω-6 PUFAs in the brain is linked to several neurological and neuropsychiatric disorders [2, 3].

One possible mechanism for the involvement of dietary PUFAs in brain health is its role in modulating the endocannabinoid system. Indeed, bioavailability of ω-6 and ω-3 PUFAs modulates brain endocannabinoids: an increase in dietary ω-6 PUFAs is associated with increased levels of anandamide and 2-AG [4–6]. In this context, our group recently demonstrated that developmental ω-3 PUFA deficiency in mice abolishes the endocannabinoid-dependent synaptic plasticity and associated signaling pathways [7, 8]. This was the first evidence that a change in dietary precursors can have a strong impact on the outcome of the endocannabinoid system. Endocannabinoids are thus in a unique position to link food lipids and synaptic activity and our working hypothesis is that the effects of dietary ω-6/ω-3 PUFAs on brain function are mediated by their modulatory actions on the endocannabinoid system.

In this chapter, PUFAs entry in the brain and metabolism linking PUFAs to endocannabinoids production will be described. Then, how dietary ω-6/ω-3 PUFAs impact on the functioning of endocannabinoid system will be reviewed. In the third part, what is known about the interactions between PUFAs and endocannabinoids in neurological and neuropsychiatric disorders will be described. Finally, we will conclude on the possible implications of the interactions between PUFAs and endocannabinoids in the brain.

2. PUFAs in the brain: metabolism and function

2.1. Entry of PUFAs in the brain and metabolism

The main PUFAs present in the brain are arachidonic acid (ARA, 20:4n-6) and docosahexaenoic acid (DHA, 22:6n-3). These two long-chain PUFAs can be directly provided by food, or metabolized from dietary precursors in the liver (**Figure 1**). Blood ARA and DHA enter the brain, probably by a free diffusion across the cell membranes of the blood–brain barrier, even active transporters may exist [3, 9–12] (**Figure 1**). Once in the brain, active processes preserve ARA and DHA in high concentrations and degrade or recycle the other types of PUFAs [13]. Some evidence also suggest active transporters with specificity for some PUFAs to regulate the levels of each PUFA in the brain [14–18].

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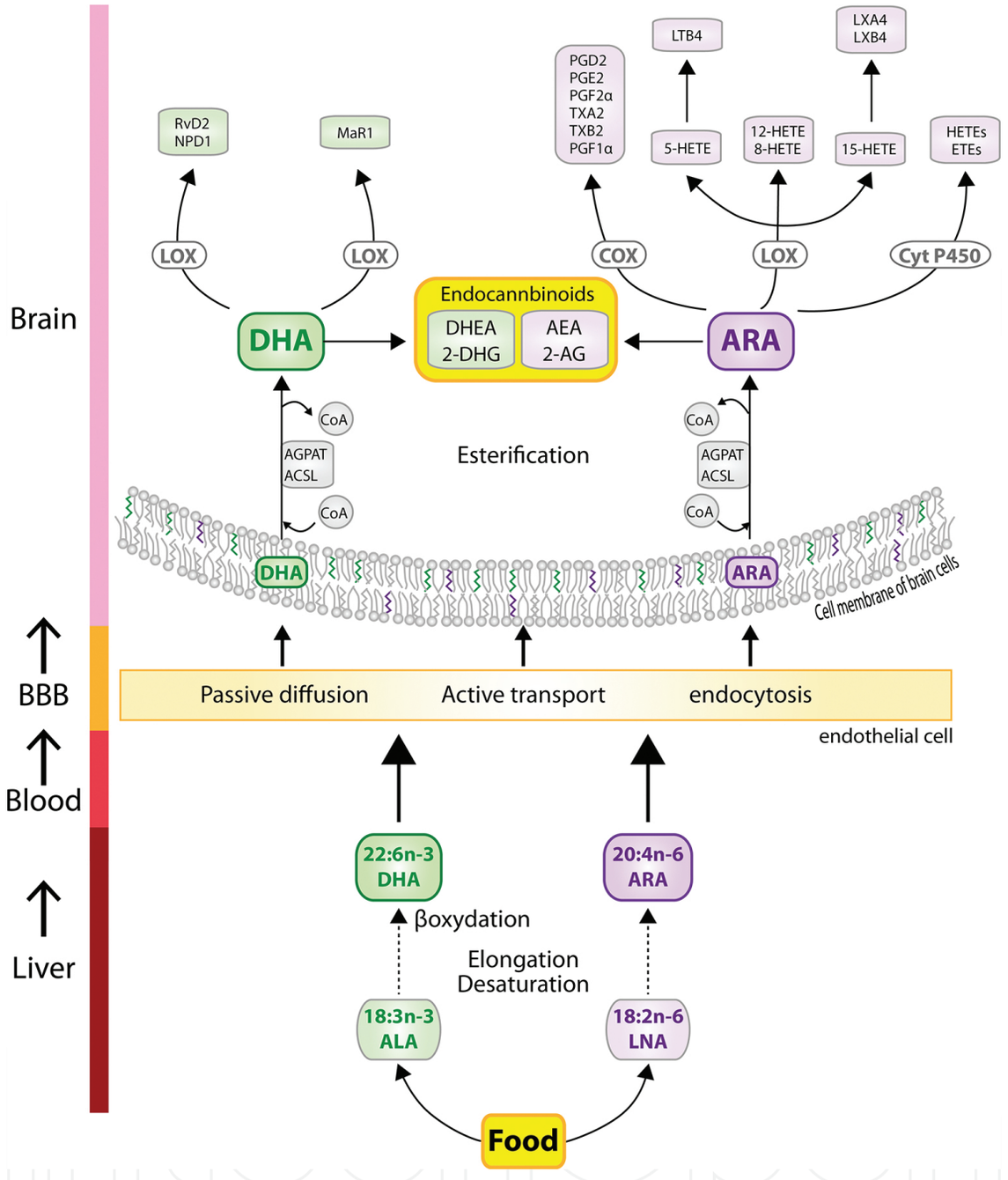


Figure 1. From PUFAs synthesis to PUFAs derivates in the brain. Precursors of ω-6 and ω-3 fatty acids are provided by food (bottom). They are metabolized in the liver into more unsaturated and elongated fatty acids (long-chain PUFAs) through successive elongation and desaturation. Long chain PUFAs, ARA (20:4n-6) and DHA (22:6n-3), then enter the brain *via* the blood and the blood–brain barrier (BBB), successively. Delivery into the brain can be made through free diffusion, active transport with specific transporters, or *via* endocytosis into the BBB endothelial cells. Once in the brain, PUFAs are esterified in phospholipids of cell membranes. When released from the membrane they are metabolized in endocannabinoids or in multiple derivates with COX, LOX and Cytochrome P450 enzymes. ALA (18:3n-3), alpha linoleic acid; LNA (18:2n-6), linolenic acid; AGPAT, 1-acylglycerol-3-phosphate-O-acyltransferase; ACSL, long-chain-fatty-acid-CoA synthase; RvD2, resolving D2; NPD1, neuroprotectin D1; Mar1, maresin 1; PGD2, prostaglandin D2; PGE2, prostaglandin E2; PGF2a, prostaglandin F2a; TXA2, thromboxane A2; TXB2, thromboxane B2; PGF1a, prostaglandin F1a; LTB4, leukotriene B4; HETE, hydroxyeicosatetraenoic acid; LXA4, lipoxin A4; LXB4, lipoxin B4; ETE, ecosatetraenoic acid.

PUFAs are constituent of plasma membranes and they accumulate into brain cells phospholipids predominantly during brain development [19]. This means that the PUFA composition of membranes in the brain is predominantly determined during cerebral development, which raises the importance of adequate ARA and DHA dietary supply during perinatal periods. At adult age, ARA and DHA supply in the brain is mainly to recycle existing pools used for PUFA metabolites and it is estimated that in humans half-life of ARA is five months, compared to two years for DHA [20]. Accordingly, it has been estimated that the brain needs 18 mg/day of ARA and 4 mg/day of DHA. Even if the developmental period is crucial for PUFAs accretion in brain membranes and therefore composition, changes in the diet or in the metabolism of PUFAs can alter the ratio between ARA and DHA at adulthood. This is particularly true in some neurological disorders such as depression, schizophrenia, Alzheimer disease or Parkinson's disease [3, 21], where the organism is not able to buffer PUFAs concentrations. In regard to the endocannabinoid system, dietary PUFAs levels have profound consequences because PUFAs are the precursors of brain endocannabinoids (**Figure 2**). In animal models fed three to four months with a diet deficient in ω-3 PUFAs, the amount of DHA in the brain is reduced by 30% [7, 8, 22–26], with a consequence on endocannabinoid system (see part 3b and **Figure 3**).

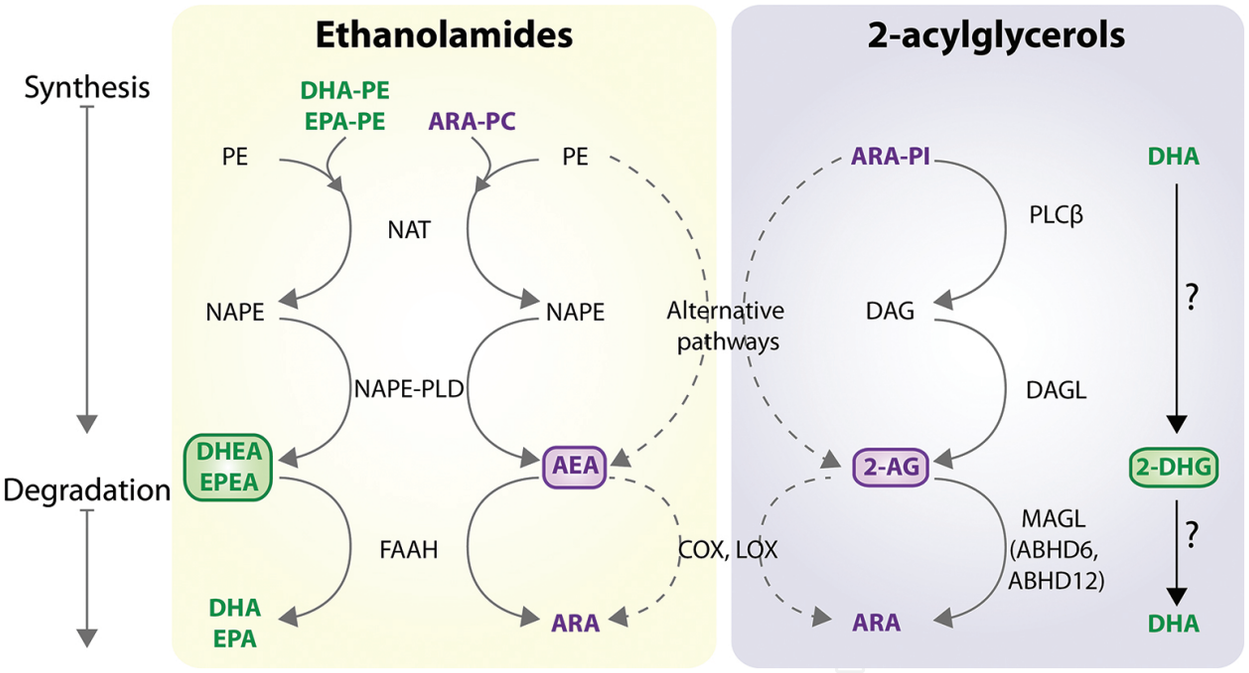


Figure 2. Metabolic pathways of the two families of endocannabinoids, ethanolamides and 2-acylglycerols. Ethanolamides are produced from PUFAs by an enzymatic pathway involving NAT and NAPE-PLD. FAAH is the main enzyme responsible for ethanolamides degradation. 2-acylglycerols are produced from PUFAs by a successive action of PLCβ and DAGL. MAGL is the main enzyme of 2-acylglycerols degradation, but ABHD6 and ABHD12 are also important degradation enzymes. For both families of endocannabinoids, alternative production pathways exist, but their characteristics and importance remain to be established. COX and LOX are other enzymes able to degrade endocannabinoids, by oxydation of their PUFA part. Synthesis and degradation pathway for 2-DHG remain mostly unknown. PE, phosphatidylethanolamine; PI, phosphatidylinositol. For 2-DHG, '?' indicates that no data exists in the literature about its metabolic pathway.

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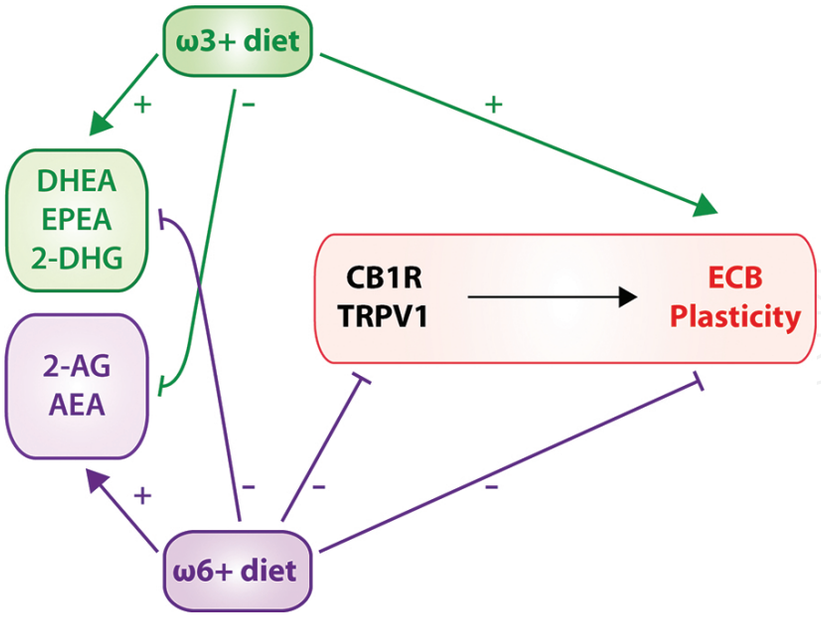


Figure 3. Effects of dietary PUFAs on endocannabinoid-dependent plasticity. In the brain of rodents fed with a diet rich in ω-6 PUFAs, 2-AG and AEA levels are increased, while ω-3-derived endocannabinoids (DHEA, EPEA and 2-DHG) are decreased. In addition, ω-6 rich diet impairs endocannabinoid plasticity and CB1 receptor (CB1R) activity. Conversely, a diet rich in ω-3 and especially DHA and/or EPA, increases levels of ω-3-derived endocannabinoids and decreases levels of 2-AG and AEA. An ω-3 rich diet positively impacts on synaptic plasticity, but the precise mechanisms remain to be determined.

Once into the brain PUFAs do not stay free in the medium, they are immediately esterified to phospholipids by specific enzymes (Figure 1). When associated to phospholipids, PUFAs play important role in the structure of membranes, by determining its curveting and flexibility [27, 28]. More importantly, PUFAs can be released by phospholipase enzymes to be metabolized by cyclooxygenase (COX) / lipoxygenase (LOX) pathways in a huge variety of derivates [3, 29–31] (**Figure 1**). These derivates are mainly involved in neuroinflammatory processes and the classical picture is that derivates from ω-6 PUFAs, in particular ARA, are pro-inflammatory whereas ω-3 PUFAs derivates, mainly EPA (ecosapentaenoic acid) and DHA, are anti-inflammatory and pro-resolutive factors. The main enzymes involved in these processes are COX, LOX and cytochrome P450 [3, 29–31]. In the brain, it is still unclear whether neurons and/or glial cells are the main cellular type involved in the production of PUFA derivates with pro or anti-inflammatory activities. Apart of inflammatory derivates, PUFAs are also precursors of endocannabinoids and this is the object of the present review (see part 2c).

2.2. Functions of PUFAs in the brain

2.2.1. Synaptic effects of PUFAs

There are various means by which PUFAs can influence synaptic function. First, as structural elements of plasma membranes, PUFAs can modulate the dynamic of membranes [27, 28, 32] and thus the functionality and traffic of transmembrane and membrane-associated proteins. These proteins are very numerous at both pre- and post-synapses (receptors,

transporters, ion channels …) and are essential for the function of the synapse. Second, PUFAs and/or their derivates are agonists of receptors with synaptic functions. This mode of action of PUFAs is very complex and hardly understood, therefore still being an intense research topic [3]. Third, PUFAs are precursors of endocannabinoids, which are lipid mediators with essential functions in neurotransmission and synaptic plasticity [33]. This will be largely developed in parts 3 and 4.

2.2.2. Role of PUFAs in neurogenesis and neuroprotection

DHA has positive effects on neuronal survival and neurogenesis [34, 35]. However, underlying mechanisms remain poorly understood. Interestingly, it has been recently discovered that synaptamide, an endocannabinoid derivate of DHA, play an important role in cellular growing and differentiation in the brain during development [36]. Neuroprotectin D1 (NPD1) is another derivate from DHA that protects against neuronal death by triggering the synthesis of anti-apoptotic proteins [37, 38]. It is also known that DHA stimulates neuronal survival by inducing the synthesis of BDNF (brain-derived neurotrophic factor) [39]. These positive effects could explain the potential benefit of DHA supplementation in neurodegenerative disorders [21, 40], but this needs to be further explored.

2.2.3. Role of PUFAs in neuroinflammation

As previously mentioned, PUFAs are precursors of an infinite variety of derivates, preferentially pro-inflammatory for ARA derivates and anti-inflammatory for DHA and EPA derivates (**Figure 1**). As a consequence, a diet rich in DHA in humans is associated with a decreased risk of developing neurological disorders with an inflammatory component, such as Alzheimer's disease or depression [41–43]. In animal models, our laboratory demonstrated that neuroinflammatory processes are over-activated in the brain of mice fed a diet deficient for ω-3 PUFAs [26, 44]. Conversely, ω-3 PUFA brain enrichment protects against deleterious effects of inflammation on cognitive performances [24, 45, 46]

3. PUFAs are precursors of endocannabinoids

Endocannabinoids are defined as endogenous lipids able to activate CB1 or CB2 cannabinoid receptors. The two major endocannabinoids described in the organism are 2-AG and anandamide (AEA). They are part of two families of endocannabinoids, 2-acylglycerols for 2-AG, and ethanolamides for AEA (**Figure 2**), but all species in these families are not ligand of cannabinoid receptors. AEA and 2-AG are the two species with the highest affinity for CB1 and CB2, and their role in neuronal plasticity has been thoroughly demonstrated [33, 47]. These two canonical endocannabinoids are derived from the ω-6 PUFA ARA and most of studies have focused on these endocannabinoids. However, more and more studies are highlighting the role of ω-3-derived endocannabinoids. These species are agonists of CB1 and CB2 receptors, but their role in neuroplasticity is yet to be unraveled.

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Briefly, there is a two-step process to form endocannabinoids from phospholipids. Endocannabinoids are made on-demand and they are rapidly degraded, back into PUFAs or oxydized into active metabolites. Interestingly, degradation enzymes are more numerous and more active than production enzymes of endocannabinoids, suggesting that endocannabinoids are highly regulated and never stay for long at the synapse [48]. This may be explained by the fast desensitization of CB1 receptor. Endocannabinoid system thus appears as a highly dynamic and regulated system.

Here, we will describe the canonical pathways for endocannabinoids production and degradation at the synapse. However, these canonical are still under debate, especially because the importance of secondary pathways is unknown [49].

3.1. 2-AG metabolism

The first step of 2-AG formation is the hydrolysis by a phospholipase C (PLC) enzyme of a phosphatidylinositol (PI) containing an ARA PUFA. In postsynaptic neurons, it is mainly the PLCβ that is involved in this process because it is activated by $G_{q/11}$-coupled receptors, such as group I metabotropic glutamate receptors or acetylcholine receptors [48, 50–52]. The product of this reaction is ARA-containing diacylglycerol (DAG). This DAG is then the substrate of a DAG-lipase enzyme (DAGL) that hydrolyzes the DAG into 2-AG (removal of the acyl group) (**Figure 2**). DAGL enzyme has two isoforms, DAGLα and DAGLβ and it is likely that DAGLα is the main enzyme responsible for the formation of 2-AG in the brain. Indeed, DAGLα is spatially close to PLCβ, and DAGLα-deficient but not DAGLβ-deficient mice display a strong reduction in 2-AG brain levels [53, 54].

Once it is formed, 2-AG exerts its action by targeting CB1 receptors on presynaptic neurons or CB2 receptors on glial cells surrounding the synapse (microglia and astrocyte). 2-AG is thus a retrograde messenger that is released from the post-synapse into the synaptic cleft. The question of an active transporter for 2-AG has been densely investigated but up to now, there is no identified transporter for 2-AG [55]. The most likely hypothesis at present is that DAGL enzyme is responsible for release of 2-AG in the synaptic cleft.

Once 2-AG binds to CB1 and/or CB2 receptors, it is rapidly processed for degradation by the enzyme MAGL (monoacylglycerol lipase) (**Figure 2**). The MAGL enzyme is present in postsynaptic astro-glial compartments [56–58] and it hydrolyzes 2-AG to form ARA and glycerol. There is some redundancy in degradation enzymes for 2-AG because ABHD6 (Abhydrolase domain containe protein 6) and ABHD12 can also hydrolyze 2-AG [48, 56]. Degradation of 2-AG can also be performed by its oxygenation with COX and LOX enzymes, which produces PUFA derivates with bioactive functions [59–61] (**Figure 2**).

3.2. AEA metabolism

Metabolism of AEA follows a similar process as 2-AG. First, the N-acyltransferase enzyme (NAT) uses the ARA of a phosphatidylcholine (PC) and a phosphatidylethanolamine (PE) to form a N-acyl-phosphatidylethanolamine product (NAPE) (**Figure 2**). Anandamide production is triggered by calcium entry into the cell, since the NAT enzyme is activated by calci-

um [62]. Sources of calcium can be diverse, mainly NMDA receptor and voltage-gated calcium channels, or alternatively release from intracellular stores. Interestingly this calcium-dependent NAT remains molecularly uncharacterized [48], which reflects the gaps in the literature that exist concerning the endocannabinoid system. The NAPE formed is then hydrolyzed in AEA by a NAPE-phospholipase D enzyme (NAPE-PLD) (**Figure 2**). Here again, this enzyme is not well characterized and many questions remain about its activity, regulation and localization [48].

Transport of AEA is better characterized than 2-AG transport, but it is still largely under debate. A FLAT transporter (fatty acid amide hydrolase-like anandamide transporter) has been discovered recently for intracellular transport of AEA [63], but a study published one year later contradicts its putative role [64]. It is thus too soon to conclude clearly on this point [49, 55]. In addition, recent studies revealed that the preferred target of AEA in the brain may be postsynaptic TRPV1 (transient receptor potential vallinoid 1) channels and not necessarily presynaptic receptors. It is thus possible that AEA does not need to travel the synaptic cleft but may act directly by travelling through the plasma membrane to activate intracellular postsynaptic TRPV1 receptors. TRPV channels are vallinoid receptors involved in nociception that are primarily activated by capsaicin [65–67]. In the brain, AEA appears as a potent agonist of TRPV1 and its role in endocannabinoid-dependent synaptic plasticity has been demonstrated [33, 68–70].

The main enzyme responsible for degradation of AEA is FAAH (fatty acid amide hydrolase) which produces an ethanolamine and an ARA PUFA (**Figure 2**). FAAH is situated in the intracellular compartment and is bound to membranes, which can modulate the access of AEA to its degradation enzyme [71]. Drugs targeting the FAAH enzyme have been extensively studied for the treatment of endocannabinoids-related disorders, such as anxiety, depression, inflammation or neuropathic pain [72]. However, pharmaceutics are struggling to find a compound with high efficiency and low side effects, which may be due to chronic effects of FAAH inhibition that differ from acute effects [73, 74] (**Figure 2**).

Contrarily to 2-AG, there is no known other enzyme for degradation of AEA, except COX and LOX enzymes that can oxygenate the ARA group of AEA to form bioactive derivates of ARA [59–61].

3.3. Alternative production pathways

One of the reasons for the complexity of the endocannabinoid system and its study is the existence of multiple alternative enzymatic pathways. Transgenic mice constitute a good tool to investigate the redundancy of a protein. Mice deficient for DAGLα have a strong decrease in 2-AG levels, while mice deficient for MAGL display very high levels of 2-AG [48, 53, 75]. This suggests that redundancy for 2-AG synthesis and degradation is not the majority. Conversely, mice deficient for NAPE-PLD have elevated levels of NAPE, but there is almost no change in AEA levels [48, 76, 77]. This suggests that NAPE-PLD is the main pathway to hydrolyze NAPE but that robust redundant mechanisms do exist to form AEA. However, these secondary mechanisms have not yet been discovered. Apart from these studies, other pathways have been described to form and degrade endocannabinoids [49]. For example, 2-

AG can be formed by hydrolysis of lyso-PI by phospholipase 1 enzyme [48]. However, the physiological significance of these secondary pathways has yet to be unraveled.

3.4. Endocannabinoids derived from ω-3 PUFAs

In the brain, 2-AG and AEA are the canonical endocannabinoids but other bioactive lipids derived from ω-3 PUFAs are ligand of CB1 and CB2 receptors. The two main ω-3 PUFAs described in the literature are ethanolamides derived from DHA, called DHEA (N-Docosahexaenoyl ethanolamine), and from EPA, called EPEA (N-Eicosapentaenoyl ethanolamine). Endocannabinoids EPEA and DHEA are present in the brain in concentrations about two fold higher compared to AEA [78], but their binding affinity for CB1 and CB2 receptors is probably lower [79, 80]. EPEA and DHEA share the exact same pathways of production as AEA, except that NAT enzyme uses respectively the EPA or the DHA group of a phosphatidylethanolamine to form the NAPE product (**Figure 2**). The ω-3-derived endocannabinoids also follow the degradation pathways of AEA, with FAAH as the main degradation enzyme, and there is the possibility for DHEA and EPEA to be oxidized by COX and LOX enzymes (**Figure 2**).

As discussed in parts 4 and 5, dietary ω-6/ω-3 ratio directly modulates the proportion of ethanolamides derived from ω-6 and ω-3, but the role of ω-3 derived endocannabinoids remains elusive. One issue that faces researchers to study the role of ω-3-derived endocannabinoids is that they share exactly the same enzymatic pathways as AEA. It is thus currently not possible to precisely target their synthesis or degradation.

So far, the role of DHEA has been demonstrated in neuronal development and synaptogenesis [36, 81, 82], but its effect is likely independent of activation of cannabinoid receptors. It exists other ethanolamides derived from monounsaturated fatty acids (such as N-oleoyl amide derived from oleic acid). They don't bind to CB1 or CB2 receptors, but they can have cannabimimetic activities. It has been suggested that these ethanolamides could serve as 'entourage molecules' to modulate the signaling of AEA [59]. Finally the ω-3 derived endocannabinoid 2-docosahexanoylglycerol (2-DHG) is sometimes evoked in the literature [83, 84], but there is a crucial lack of data about the enzymatic pathways and the binding affinity of this bioactive lipid (**Figure 2**).

4. Impact of dietary ω-6/ω-3 on the endocannabinoid system

4.1. What do we know from research at the periphery

At the periphery, endocannabinoids receptors are mostly present in adipose tissue, immune system, musculoskeletal system, gonads and cardiovascular system. All of these compartments are also regulated by dietary PUFAs. Because PUFAs are precursors of endocannabinoids, the effect of dietary PUFAs on endocannabinoids in these compartments has been relatively well documented [85–92]. Consistently, it appears that increasing dietary ω-6 PUFAs does increase levels of ARA-derived endocannabinoids in the organism (**Figure 3**). Conversely, diets enriched in ω-3 decreases ARA-derived endocannabinoids (AEA and 2-AG) while it

increases levels of endocannabinoids derived from ω-3 PUFAs, namely DHEA and EPEA (**Figure 3**). However, studies have rarely investigated the functional consequences of this link between dietary PUFAs and levels of endocannabinoids. There is a strong hypothesis that beneficial effects of ω-3 supplementation pass through an effect on the endocannabinoid system, but it has never been directly tested.

In details, the impact of dietary PUFA on endocannabinoids has been investigated in the context of obesity. Indeed, activation of CB1 receptors in adipose tissue increases food intake and increases the creation of new adipocytes [93]. Endocannabinoids are thus a target to treat obesity [94]. Rimonabant, an antagonist of CB1 receptors, has been used in overweighed patients to reduce their food intake, with very positive results. However, strong side effects on mood for some patients lead to the withdrawal of rimonabant from the market. In this context, dietary PUFAs appeared as homeostatic regulators of endocannabinoids [95], encouraging researchers to investigate the effect of ω-3 rich diet on obesity. It has been shown that a diet rich in ω-3 leads to weight loss, in parallel to a decrease of AEA and 2-AG [88, 93]. Interestingly, a high fat diet rich in ω-3 does not induce weight gain, while a low fat diet rich in ω-6 increases weight gain [89, 90, 96]. These evidence suggest that dietary PUFAs act on fat formation and thus on weight gain *via* the endocannabinoid system. This hypothesis has been reinforced by a study showing that blockade of CB1 receptor (with rimonabant) blocks weight gain induced by high fat diet [96]. However, evidence remains indirect and we can hardly conclude that the endocannabinoid system is the only pathway by which dietary PUFAs influence weight gain and adipose tissue formation.

Inflammation is another component of obesity that can be modulated by endocannabinoids and PUFAs. Endocannabinoids are homeostatic regulator of the immune system and their oxydized metabolites (directly derived from PUFAs) can have a direct role in inflammation [97]. In parallel, the role of PUFAs on inflammation is well documented [98, 99]. Globally, we can summarize that ω-6 PUFAs, such as ARA, are metabolized in pro-inflammatory derivates while ω-3 PUFAs, such as DHA and EPA, are metabolized in anti-inflammatory and pro-resolution derivates [3, 29–31]. PUFAs play thus a central role in the immune response of the organism. However, very little is known about the interactions between PUFAs and endocannabinoids in the peripheral immune system.

Concerning the musculoskeletal compartment, evidence exists for a correlation between dietary ω-6/ω-3 ratio and levels of ARA- and ω-3-derived endocannabinoids [91, 100, 101]. More interestingly, addition of free ω-3 in the culture medium of osteoblastes changes the level of proteins of the endocannabinoid system: CB2 receptors and NAPE-PLD [101]. Moreover, a diet enriched with DHA for 2 to 4 months increases expression of CB1 and CB2 receptors in muscles, and it favors glucose uptake by the muscle and not by the adipose tissue [91]. It thus appears that in the musculoskeletal system, dietary PUFAs could affect not only endocannabinoid levels, but also the regulation of the proteins of the endocannabinoid system.

In the field of cardiovascular health, it is recognized that both endocannabinoids and ω-3 PUFAs have beneficial effects [102, 103], but the link between endocannabinoids and PUFAs has never been investigated to our knowledge. Of note, we found one review paper suggest-

ing that ω-3-derived endocannabinoids could be beneficial for heart function [102], but this hypothesis remain to be tested.

Finally, there is an emerging role of endocannabinoids in gonadic function and more largely in the control of fertility [104–106]. Endocannabinoids and associated receptors are present in female and male gonads and they play a role of fertility signal in the reproduction cycle. In addition, endocannabinoids can regulate gonadic hormones [106]. As a consequence, an aberrant endocannabinoid signaling impairs fertility at all stages [104]. In parallel, PUFAs also play important role in fertility and especially in function of spermatozoa. Indeed, testis and sperm are very rich in DHA and the high concentration of PUFAs —DHA in particular— is necessary for optimal motility and thus fertility of germ cells [92, 107, 108]. It is suggested that PUFAs are necessary to sperm function due to their role in membrane fluidity, however, the hypothesis that PUFAs play a role in sperm fertility *via* their endocannabinoids metabolites has not yet been explored clearly.

Generally, we can conclude from these studies that modulating dietary PUFAs inevitably modulates levels of endocannabinoids in the organism. In addition, it often emerges from these studies the idea that it exists 'good endocannabinoids' and 'bad endocannabinoids'. In this concept, ARA-derived endocannabinoids need to be down-regulated in pathological states (obesity, inflammation, etc.), and a diet rich in ω-3 decreases the levels of ARA-derived endocannabinoids (the 'bad' one), in favor to ω-3-derived endocannabinoids (the 'good' one). This appealing hypothesis needs to be studied because the presence of ω-3-derived endocannabinoids in the organism is known, but their function remains to be fully investigated.

4.2. Impact of dietary ω-6/ω3 PUFAs on endocannabinoid levels in the brain

Similar to studies at the periphery, dietary ω-6 PUFAs increases levels of 2-AG and AEA in the brain (is this where levels are increased?), while dietary ω-3 PUFAs increases levels of ω-3-derived endocannabinoids (**Figure 3**). Specifically in the brain, a first study in 2001 compared diets with or without PUFAs on ethanolamides, without distinguishing ω-3 and ω-6 [4]. In this study, three weeks of diet deficient for PUFAs was enough to reduce levels of ethanolamides in piglet brains. Interestingly, levels of ethanolamides were strongly affected in brainstem, cerebellum, visual cortex and striatum, while they were unaffected in visual cortex and hippocampus. Two years later, another study focused on ω-3 PUFAs content of the diet and its impact on 2-AG in mouse brain [5]. In this study, analysis was done on mice fed with one or the other diet for two generations. As expected, brain levels of 2-AG were increased by a diet rich in ω-6 and they were decreased by a diet rich in ω-3. More interestingly, DHA brain levels were modified by the diet, while ARA, the precursor of 2-AG remained perfectly stable. Indeed, consistently in the literature, ARA levels are hardly modified by PUFAs content of the diet, while DHA brain levels are easily correlated to dietary ω-6/ω-3. This suggests that ARA levels in the brain are highly controlled to maintain homeostasis and increase in 2-AG and AEA following ω-6 rich diet could be one way of buffering ARA concentrations. More recently, a dietary experiment has been conducted on rats with only one week of diet at adult age and no difference has been found compared to the control diet [6]. Another study with two weeks

of DHA-rich diet showed increased levels of DHEA and decreased levels of AEA, without changes on 2-AG levels [78].

These studies confirm that dietary PUFAs modulate levels of endocannabinoids in the brain, as well as in the periphery. However, the function of the endocannabinoid system in the brain depends also on the ability of the signaling machinery to trigger the appropriate production of endocannabinoids, on the functionality of the receptors, and on the function of degradation enzymes.

4.3. Impact of dietary ω-6/ω3 PUFAs on proteins of the endocannabinoid system

Very little is known about modifications of the endocannabinoid system in the brain due to dietary PUFAs. A recent study examined the impact of ω-3 deficient diet on enzymes implicated in the metabolism of PUFAs, but not concerning directly the endocannabinoid system [22]. In this study, 15 weeks of ω-3 deficient diet modified the levels of phospholipases A2 and COX enzymes, to favor degradation of ARA and reduce the metabolism of DHA. This suggests that imbalanced PUFAs content in the diet are compensated by enzymatic processes in the brain, but the question remains open for enzymes of the endocannabinoid system. One study reported that DHA supplementation increases levels of CB1 and TRPV1, in terms of mRNA expression and protein levels [109] (**Figure 3**). Recently, our laboratory demonstrated that a dietary ω-3 deficiency from gestation induces a desensitization of the CB1 receptor [7, 8] (**Figure 3**). We hypothesize that this is due to high levels of 2-AG and AEA produced by developmental ω-3 deficiency, but this remains to be fully investigated. Our results have been reinforced by a recent study showing that a diet with 5% krill oil (rich in EPA and DHA) given for six weeks to adult mice enhanced the activity of CB1 receptor [110]. It is known that the CB1 receptor can be easily desensitized and internalized by its ligand [111]. This has been particularly studied in the context of chronic cannabinoid consumption to decipher the mechanisms of addiction. Mechanisms of desensitization and downregulation are not totally elucidated but they probably involve phosphorylation of the receptor and transcription of immediate early genes [112, 113]. Interestingly, CB1 receptors do not desensitize at the same rate, depending on the brain structure [113]. Studies on the role of dietary PUFAs on CB1 receptors demonstrate that dietary PUFAs can constitute another powerful mechanism for regulation of the functionality of the CB1 receptor.

4.4. Impact of dietary ω-6/ω-3 PUFAs on endocannabinoid-dependent synaptic plasticity

In the brain, synaptic plasticity is the main measurable outcome of the functionality of the endocannabinoid system. Indeed, endocannabinoids act to reduce the synaptic efficacy, at very short, medium, or long periods of time, depending on the signaling pathways that trigger endocannabinoid production. As we described above, endocannabinoids are produced on-demand *via* activation of specific enzymes depending on the endocannabinoid produced [33]. Released endocannabinoids then activate receptors, which leads to a decrease of efficacy of the synaptic transmission [33]. Importantly, endocannabinoids are rapidly degraded and released PUFAs are re-esterified at the membrane, to precisely regulate duration of endocannabinoid action [27]. This general principle of action of endocannabinoid at the synapse is

developed in a wide variety of mechanisms, depending on the structure and the triggering event, and it induces plasticity phenomenon lasting for seconds to hours [33, 56, 114] but always in the direction of a decrease of synaptic efficacy. Very recent studies suggest that endocannabinoids can also act to increase synaptic efficacy [115, 116], but mechanisms remain unclear so it can be an indirect consequence of an endocannabinoid activation.

Some studies have investigated the link between dietary PUFAs and synaptic plasticity [44, 82, 117, 118]. It appears that ω-3 PUFA dietary deficiency impairs glutamatergic synaptic transmission and plasticity [44, 82, 117, 119, 120], whereas DHA-rich diet can prevent loss of synaptic plasticity induced by prenatal ethanol exposure [118] (**Figure 3**). Apart from these studies, only one study from our laboratory precisely investigated the impact of dietary PUFAs on the endocannabinoid-dependent synaptic plasticity [7]. This study demonstrated that developmental dietary ω-3 PUFA deficiency abolishes the endocannabinoid-dependent synaptic plasticity in the prefrontal cortex and in the nucleus accumbens [7]. This is the first evidence that a change in dietary precursors can have a strong impact on the outcome of the endocannabinoid system. Following this study, we investigated the impact of developmental dietary ω-3 PUFA deficiency on endocannabinoid-dependent synaptic plasticity in the hippocampus. We demonstrated that ω-3 PUFA deficiency strongly impaired the endocannabinoid-dependent heterosynaptic plasticity at GABAergic synapses, which prevents the induction of plasticity at glutamatergic synapses (Thomazeau, Bosch-Bouju, Manzoni and Layé, article accepted at Cerebral Cortex). Conversely, another ongoing study from our team shows that ω-3 PUFA-rich diet maintains endocannabinoid-dependent Hebbian plasticity in the nucleus accumbens following a chronic social defeat stress. Mechanistically, it is still unclear how dietary PUFAs impact on endocannabinoid plasticity. As evoked above, dietary PUFAs can change levels of endocannabinoids. This could impact on the endocannabinoid system and notably on the CB1 receptor that easily desensitizes. Along with this hypothesis, we demonstrated in our recent study that the loss of plasticity following ω-3 PUFA deficiency was due to a loss of functionality of the CB1 receptor, by its uncoupling from the Gi protein [7, 8] (**Figure 3**).

Other hypotheses need to be explored to better understand the impact of dietary PUFAs on endocannabinoid plasticity. Notably, it is suggested that endocannabinoid signaling is sensitive to the lipid environment, namely, the levels of lipid rafts in the membrane [121–123]. Lipid rafts are high density domains rich in sphingolipids and cholesterol [124]. It has been proposed that synapses are especially enriched in lipid rafts and that these microdomains are necessary to maintain synapses and allow protein trafficking [125]. At the opposite of lipid rafts are DHA-rich domains; they are thin, 'leaky', dynamic and flexible [126]. This is notably due to the high flexibility of DHA. High density lipid rafts and low-density DHA-domains are competing permanently. It is suggested that lipid rafts are initially small nanodomains that organize together to form bigger domains, of the microscale. In this configuration, the organization of lipid rafts would be controlled by DHA, which aggregates nanodomains together or conversely disrupt large lipid rafts [126–128]. We can thus hypothesize that dietary PUFAs modulate the endocannabinoid plasticity in the brain by playing on the fine structure of plasma membranes.

5. Dietary ω-6/ω-3 PUFAs and the endocannabinoid system: implication for neurological disorders

Studying the impact of dietary PUFAs on brain endocannabinoids is of interest in the context of brain disorders. It exists dense literature about the role of dietary PUFAs on brain health, and endocannabinoids are implicated in numerous brain diseases. However, the link between dietary PUFAs and endocannabinoids in the context of brain disorders has been only rarely investigated.

5.1. PUFAs / endocannabinoids interactions in mood and anxiety disorders

On one hand, dietary PUFAs appear to be determinant for the regulation of mood and anxiety disorders. In humans, the risk of developing depression is associated with low content of ω-3 in the diet [129], and patients with mood and/or anxiety disorders have lower levels of ω-3 in the blood and in the brain, compared to healthy subjects [3, 130–132] (**Figure 4**). Supplementation of food supply with ω-3 PUFAs constitutes thus an interesting strategy for the prevention and treatment of mood and anxiety disorders, in particular because of the low side effects expected compared to pharmacological agents. Several trials have been conducted in this context, however, meta-analyses reported mitigated outcomes so far [129, 133]. Some trials showed no convincing effect while others demonstrated that ω-3 supplementation for 8-12 weeks have significant positive effects, notably because it improves the efficiency of antidepressants and thus increases the proportion of remission [134]. The lack of clear effect of ω-3 supplementation to treat mood and anxiety disorders in humans can be explained by the complexity of neuropsychiatric disorders and the heterogeneity of methods in the different studies. As an example, a recent study highlighted the positive effect of EPA treatment in patients suffering from major depression homogenized on the basis of their inflammatory status [43]. The clinical studies are corroborated by preclinical studies. Dietary ω-3 deficiency in rodents induces strong anxiety- and depressive-like behaviors [7–9, 135–137]. Conversely, ω-3 supplementation given beforehand a protocol of acute or chronic stress plays a protective role against anxiety- and depressive-like behaviors [136, 138, 139].

On the other hand, the role of endocannabinoids system in the regulation of mood and anxiety disorders has recently raised much interest in preclinical studies. The first evidence came from behavioral studies showing that mice lacking the gene for CB1 receptor display strong depressive and anxiety-like behaviors, which can be reproduced in control mice with CB1 receptor antagonists [140, 141]. Inversely, depressive- and anxiety-like behaviors induced by acute or chronic stress are associated with alteration of AEA and 2-AG levels [142, 143], CB1 receptor desensitization [144, 145] and impairment of endocannabinoid-dependent synaptic plasticity [144, 146, 147]. Recently, we conducted a study in this context demonstrating that a chronic social defeat stress in mice totally abolished spike-timing endocannabinoid-dependent synaptic plasticity. In humans, it is established that patients suffering from mood and anxiety disorders have lower levels of endocannabinoids in blood [148]. Even if cannabis has been used for decades as a self-medication to dampen stress and anxiety, only few clinical studies so far have tried enhancement of endocannabinoid signaling as a potential therapeu-

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tics to treat mood and anxiety disorders [149, 150]. This may be due to the potential side effects of directly targeting the endocannabinoid system, and in this context dietary PUFAs, as homeostatic regulators of endocannabinoids [95], could constitute a very interesting and promising therapeutic candidate to target the endocannabinoid system.

From these studies, it thus appears that both dietary PUFAs and endocannabinoids play a role in mood and anxiety disorders and the link between both has been made only in our laboratory in preclinical studies. We demonstrated that an ω-3 deficient diet from the first gestational stage greatly impairs endocannabinoid signaling, which is associated to anxiety and depressive-like behaviors in mice [7, 136]. Currently, our ongoing studies tend to demonstrate that DHA-rich diet protects mice from deleterious effects of a chronic social defeat stress on anxiety- and depressive-like behaviors and on endocannabinoid-dependent synaptic plasticity. At long-term, we believe these studies will constitute a solid argument to investigate the effect of ω-3 supplementation to normalize endocannabinoid levels in patients suffering from anxiety or depressive disorders.

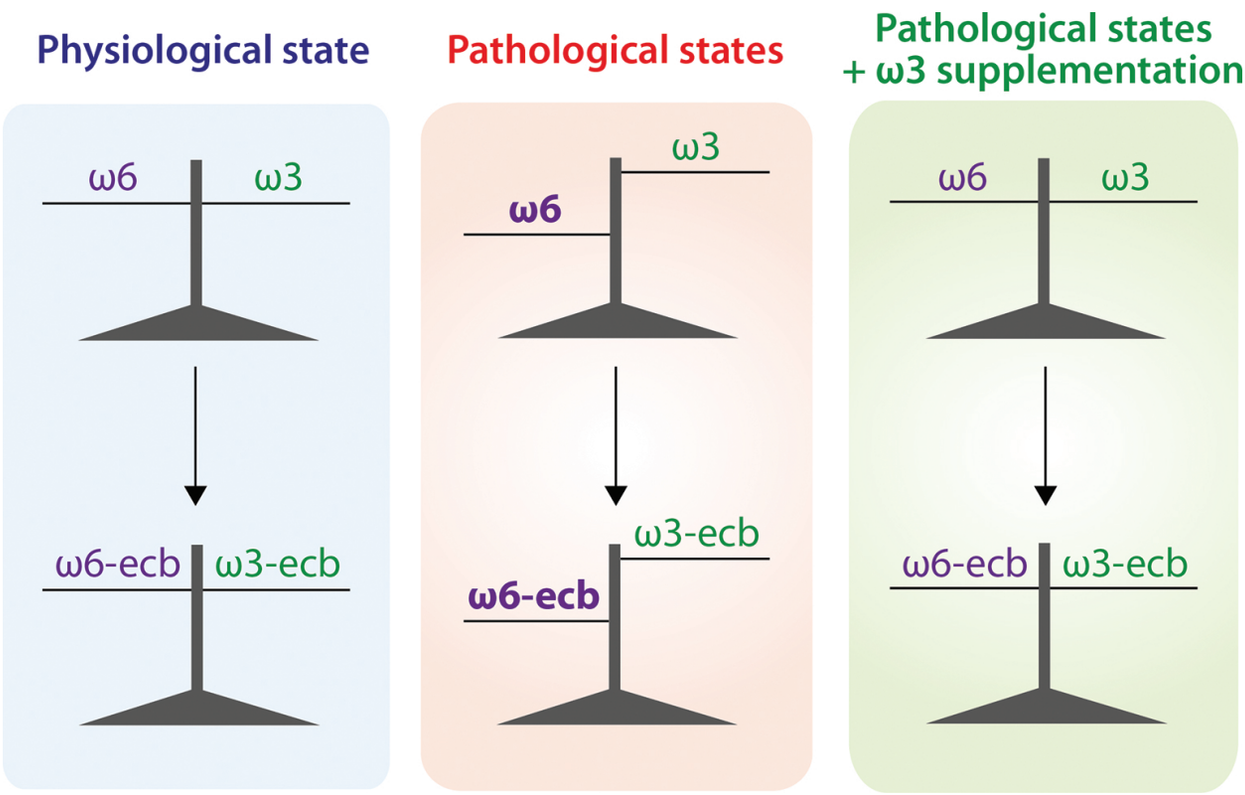


Figure 4. PUFA/endocannabinoid interactions in the pathological brain: an hypothesis. In the normal brain, (left panel), ω-6, ω-3 PUFAs and endocannabinoids derived from ω-6 and ω-3 are present in physiological concentrations. In pathological conditions (middle panel) such as mood disorders, autism, schizophrenia, neuropathic pain or neurodegenerative diseases, there is an imbalance between ω-6 and ω-3 in favor of ω-6, independently of the diet. This leads to an imbalance in brain endocannabinoids in favor of AEA and 2-AG which can potentially contribute to the physiopathology of the disease. Dietary supplementation with ω-3 PUFAs reduces ω-6/ω-3 imbalance induced by brain disorders (right panel). This normalization could normalize levels of endocannabinoids derived from ω-6 and ω-3 and contribute to prevent/treat the disorder.

In the investigation of the interactions between endocannabinoids and dietary PUFAs in mood and anxiety disorders, we also need to consider the HPA (hypothalamus-pituitary-adrenal) axis. Indeed, dietary PUFAs are powerful modulators of the HPA axis, and function of endocannabinoids is also tightly related to the HPA axis. Our studies demonstrated that variations in dietary ω-3 PUFAs impact on the HPA axis [136, 151]: mice fed with an ω-3 PUFA deficient diet exhibit higher levels of corticosterone while mice fed with a DHA rich diet display control levels of corticosterone, and these levels are not affected by social defeat stress. In parallel, interactions between endocannabinoids and the HPA axis are reciprocal. Studies have shown that glucocorticoids can activate the release of endocannabinoids, AEA and 2-AG [152]. Conversely, endocannabinoids act efficiently to regulate stress response, partly by modulating the glucocorticoid system [150, 153]. For future studies, it is thus crucial to consider the HPA axis as a potential intermediate between dietary PUFAs and endocannabinoids in the context of depressive and anxiety disorders.

5.2. PUFAs / endocannabinoids interactions in neurodegenerative diseases

In Parkinson's disease, endocannabinoids seem to play a protective role by decreasing the oxidative stress [154]. Similarly, ω-3 rich diet improves survival of dopaminergic neurons in rodent models of the disease with MPTP (1-méthyl-4-phényl-1,2,3,6-tétrahydropyridine) injections or α-synuclein transgenic mice [155–159] (**Figure 4**). In patients, levels of AEA in the cerebrospinal fluid are increased, and the risk for Parkinson's disease is increased by ω-6 rich diet, and decreased by ω-3 rich diet [42, 160]. However, clinical trials with either dietary PUFAs or with drugs targeting the endocannabinoid system have shown inconsistent results [154]. In this pathology too, it would be interesting to investigate if endocannabinoids derived from ω-3 are of potential interest to protect neurons from degeneration and improve quality of life of patients (**Figure 4**).

In Alzheimer's disease, implication of both endocannabinoids and dietary PUFAs are not central in the study of the physiopathology, still, there are interesting ways to investigate. In animal models, ω-3 PUFA supplementation clearly improves cognition and associated neurobiological markers [21, 45, 46, 161, 162] (**Figure 4**). However, clinical trials did not provide convincing results and further investigation are thus needed [3, 21, 163]. Endocannabinoids are also trialed as potential therapeutics to treat Alzheimer's disease, because they can act on multiple aspects of the disease, but no strong result has emerged from these trials yet.

From our perspective it is interesting to note that both PUFAs and endocannabinoids could interfere with the development of the disease by dampening neuroinflammation and oxidative stress. We thus believe these are the two neurobiological aspects of the disease that have to be studied to determine if dietary PUFAs can act *via* the endocannabinoid system to improve health of patients.

5.3. PUFAs / endocannabinoids interactions in physical pain

The role of endocannabinoids in neuropathic and physical pain has been clearly established [164, 165]. Indeed, endocannabinoids have the ability to lower the excitability of nociceptors

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and thus reduce the intensity of the nociceptive information [165]. A recent study interestingly demonstrated that ω-3 rich diet was able to reduce physical pain and that this relief was significantly correlated to an increase in DHEA and 2-DHG, the two DHA-derived endocannabinoids [84] (**Figure 4**). This reinforces the hypothesis that ω-3 dietary PUFAs favor 'good' endocannabinoids, derived from ω-3 PUFAs (**Figure 4**). As proposed by Piomelli et al., [165], the links between endocannabinoids and dietary PUFAs in the context of pain are probably related to inflammatory processes and this is another way to explore.

6. Perspectives: implications for future therapeutics of endocannabinoid modulation by dietary PUFAs

In 1996, a study demonstrated that lithium, a mood stabilizer used for bipolar disorders, decreases recycling of ARA, COX2 activity and levels of prostaglandins [166]. Similar effects have been reported with other mood stabilizers and antipsychotic molecules. Metabolism of ARA could thus serve as a marker for the development of new molecules for the treatment of mood and anxiety disorders.

As we mentioned above, supplementation with ω-3 PUFAs in the treatment of mood and anxiety disorders have provided mitigated results, but this could be due to the low turnover of PUFAs in the brain [20]. A possibility to bypass this issue would be to accelerate the bioavailability of PUFAs to the brain, by direct injection of free or esterified PUFAs into the brain. A preclinical study in rat demonstrated that an injection of DHA can reduce seizure score within one hour or one day, where three months are needed to reach the same result through the diet [167–169]. These promising results could be applied in the future to humans to reduce damages following stroke or reduce seizure events, but further investigations are needed before such clinical trials.

Another field that needs to be explored to our opinion is the role of dietary PUFAs on endocannabinoids during brain development. As mentioned in this chapter, PUFA accretion in the brain occurs largely during brain development and our laboratory published many articles on the effects of imbalanced dietary PUFA during development on the adult brain [3, 7, 26]. In parallel, increasing evidence highlights that endocannabinoid signaling is essential for brain wiring [170, 171]. Notably, endocannabinoids and CB1 receptors serve as guidance signals for axon cone growth [171]. The link between dietary PUFA and endocannabinoids is not yet clearly established, but it is very likely that effects of imbalanced PUFAs during development has strong consequences on the role of endocannabinoid as guidance molecules during brain wiring. This can have strong implication for brain disorders with developmental origin, such as schizophrenia.

In conclusion, dietary ω-6/ω-3 PUFAs appears as potent modulators and homeostatic regulators of endocannabinoids in the brain. The consequences of this modulation need to be investigated to understand its putative role in brain health and diseases (in particular those with endocannabinoid impairment) and develop future therapeutics to target the endocannabinoid system through dietary ω-6/ω-3 PUFAs. The most promising hypothesis that needs to

be explored to our opinion is that dietary PUFAs could switch the system from 'bad' (ω-6-derived) endocannabinoids to 'good' (ω-3-derived) endocannabinoids.

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