BBA - Biomembranes xxx (xxxx) 184033

Contents lists available at ScienceDirect

BBA - Biomembranes

journal homepage: www.elsevier.com/locate/bbamem

Review

The synaptic lipidome in health and disease

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ARTICLE INFO

Keywords:
Synapse
Dendritic spine
Plasma membrane
Lipid metabolism
Brain metabolism
Brain homeostasis
Synaptopathies

ABSTRACT

Adequate homeostasis of lipid, protein and carbohydrate metabolism is essential for cells to perform highly specific tasks in our organism, and the brain, with its uniquely high energetic requirements, poses singular characteristics. Some of these are related to its extraordinary dotation of synapses, the specialized subcelluar structures where signal transmission between neurons occurs in the central nervous system. The post-synaptic compartment of excitatory synapses, the dendritic spine, harbors key molecules involved in neurotransmission tightly packed within a minute volume of a few femtoliters. The spine is further compartmentalized into nanodomains that facilitate the execution of temporo-spatially separate functions in the synapse. Lipids play important roles in this structural and functional compartmentalization and in mechanisms that impact on synaptic transmission. This review analyzes the structural and dynamic processes involving lipids at the synapse, highlighting the importance of their homeostatic balance for the physiology of this complex and highly specialized structure, and underscoring the pathologies associated with disbalances of lipid metabolism, particularly in the perinatal and late adulthood periods of life. Although small variations of the lipid profile in the brain take place throughout the adult lifespan, the pathophysiological consequences are clinically manifested mostly during late adulthood. Disturbances in lipid homeostasis in the perinatal period leads to alterations during nervous system development, while in late adulthood they favor the occurrence of neurodegenerative diseases.

1. Introduction

Lipids are fundamental components of mammalian cells, the second major component of cellular mass after water [1]. Lipids spatially define the plasma membrane of cells, are the main structural components of myelin, constitute a reservoir of cellular energy, participate in membrane protein compartmentalization and anchoring, and mediate communication and signaling between and within cells [1]. Among lipids classes, the major components of biological membranes are glycerophospholipids, sphingolipids, plasmalogens, and sterols. Their dynamics control cell membrane fluidity and permeability and thus affect cellular processes. Furthermore, posttranslational modification of glycerophospholipids allows membrane proteins to anchor to the membrane surfaces and is implicated in controlling lipid raft partitioning, signal transduction, and targeting to the apical membrane [2].

Synapses are enriched in specific lipids, particularly cholesterol and sphingolipids [3], two lipid species that are critical determinants of membrane viscosity and indirectly control the mobility of other membrane molecules [4,5]. Cholesterol has the ability to undergo transbilayer flip-flop and thus play a role in membrane remodeling [6]. In addition to their function as structural membrane constituents, cholesterol and sphingomyelin contribute to function through the modulation of critical synaptic proteins [7–10]. Sphingolipids and cholesterol are also major substrates for the biosynthesis of myelin sheaths by oligodendrocytes [11]. The endocannabinoids, another group of lipids, also play an important role in the synapse, contributing to the regulation of many synapse-resident ion channel proteins, neurotransmitter receptors, and transporters [12,13]. In addition, endocannabinoids constitute energy conservation molecules, since they can increase energy intake and decrease energy expenditure by controlling the activity of peripheral and central neural pathways responsible for energy storage and usage [14]. Plasmalogens also participate in the assembly and function of many transmembrane transport proteins and ion channels [15]. They are thus required for the adequate function of these integral membrane proteins and also for the generation of second messengers [16]. Plasmalogens are considered to be endogenous antioxidants [17].

The ability of the brain to dynamically adapt throughout life is facilitated by constant remodeling of its architectural connectivity, a process referred to as synaptic plasticity [18]. This process involves developmentally associated changes in the lipidome of the neuron and

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https://doi.org/10.1016/j.bbamem.2022.184033
Received 3 May 2022; Received in revised form 2 August 2022; Accepted 8 August 2022
0005-2736/© 20XX

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glial cells. It is most dramatically realized at the dendritic spine level, where remodeling involves profound short- and long-term changes of the post-synaptic apparatus and of the post-synaptic density (PSD) and its molecular constituents. For instance, both the number and distribution of neurotransmitter receptors and scaffolding proteins are modified during the processes of short-term (STP) and long-term potentiation (LTP, also termed metaplasticity), two phenomena that have been associated with learning and memory formation processes [19] and involve extensive morphological remodeling of the dendritic spine. These processes require rapid turnover of lipids and a fine regulation of brain energy expenditure. Inadequate energy supplies will directly and/or indirectly impact on the synthesis of the metabolic substrates (lipids, proteins, and amino acids) required for the dendritic spine membrane to dynamically adapt to the functional requirements of the synapse, and this deficiency is associated with pathological conditions ("synaptopathies") that will be exemplified in this review.

Inborn alterations in lipid metabolism have been associated with almost 150 Mendelian diseases and with over 80 diseases that involve complex lipid biosynthesis and remodeling [20].

Although the lipid profile in humans suffers relatively small variations through the adult lifespan, it is clear that lipid metabolism undergoes a progressive deterioration with aging, most notably at advanced stages of life [21]. These modifications of brain lipids surmounted on the physiological aging process [22] induces membrane physicochemical modifications brought about for instance by the slow and steady increase in saturated fatty acids at around the age of 70, with a concomitant decrease in the levels of the unsaturated arachidonic n-6 (AA) and docosahexaenoic n-3 (DHA) fatty acids [21]. Plasmalogens and cholesterol have been reported to decrease as a result of aging [23]. Furthermore, changes in the composition of intracellular membrane compartments as a consequence of altered lipid metabolism have been reported to be a common biomarker of several neuronal disorders [24,25].

In this review we discuss the important contribution of lipids to synapse structure and function and provide examples of how alteration of lipid components of the plasma membrane may affect several physiological mechanisms and lead to pathophysiological processes that alter synapses -the so-called synaptopathies- present in several neurodevelopmental and neurodegenerative diseases of the central nervous system.

2. Brain energy expenditure along development

The brain is the organ with the highest energy consumption in our organism, using glucose (Glu) as a primary substrate and reaching values as high as 60 % of the body's basal energetic requirements during childhood. This is not surprising considering that the brain volume increases significantly during the first two years of life. This extraordinary energy demand is necessary for the brain to establish the neuronal networks required for sensory, cognitive, and motor skills. This is evidenced, for instance, in the rates of Glu oxidation and consumption in the human brain cortex, which can reach levels of about 0.4 μmol/min/g of tissue. Glu is necessary to produce adenosine triphosphate (ATP), the key intracellular energy transfer molecule universally involved in essentially all energy-dependent physiological phenomena. In the brain, Glu is also needed for neurotransmitter synthesis and synaptic function. Glu enters the brain via different Glu transporters across the blood brain barrier (BBB) and is utilized by neurons, astrocytes, microglia, and oligodendrocytes. The BBB is critical for the maintenance of brain homeostasis since it controls the accessibility of substances to and from the brain and provides a physical barrier against potentially harmful substances and most microorganisms.

During brain development, aerobic glycolysis is the prevalent metabolic pathway used for the biosynthesis of cell constituents such as brain lipids required for synapse formation and myelination [26,27]. As a supplementary substrate for energy production the brain can utilize fatty acid oxidation that generates ketone bodies (KBs) [28]. Cholesterol and fatty acids constitute 50 % of the gray matter in brain [29] and use ketones as a substrate for their synthesis. Ketone catabolism is an indispensable source of energy [28], providing acetoacetyl-CoA and acetyl-CoA for the synthesis of cholesterol, fatty acids, and complex lipids (Fig. 1).

Glycolysis and ketolysis deliver the substrates for neurotransmitter and lipid synthesis to the mitochondria. These processes provide pyruvate, acetyl-CoA, α-ketoglutarate and citrate. Citrate is key substrate for lipid and neurotransmitter synthesis (e.g., choline and acetylcholine). By the action of several enzymes citrate can be converted to cholesterol, phospholipids and sphingolipids, all necessary as plasma membrane components and for myelin synthesis. Cholesterol synthesis in the brain occurs mainly in astrocytes via the Bloch pathway and to a lesser extent in neurons via the Kandutsch-Russell pathway. In both pathways, cholesterol synthesis is initiated via the conversion of acetyl-CoA to lanosterol but differs in the precursors involved: desmosterol in the Bloch pathway and 7-dehydrocholesterol in the Kandutsch-Russell pathway. Abbreviations used: HMG-CoA, 3-hydroxy-3-methyl-glutaryl CoA; farnesyl-PP, farnesyl diphosphate; AA, arachidonic acid; ECB, endocannabinoids; DHA, docosahexaenoic acid; SQLE, squalene monooxygenase. Created using Servier Medical Art Commons Attribution 3.0 Unported License (http://smart.servier.com). Servier Medical Art by Servier is licensed under a Creative Commons Attribution 3.0 Unported License.

At the early postnatal period, both acetoacetate and β-hydroxybutyrate are the preferred substrates for the synthesis of phospholipids and sphingolipids, in line with brain growth and myelination requirements. Accordingly, the proportion of KB incorporated into these lipids increases during the first weeks of postnatal development as the accumulation of cholesterol and phospholipids accelerates in the brain [28].

Late adulthood is a period of life when neurodegenerative diseases like Alzheimer disease (AD) of the sporadic or late-onset form (LOAD) or Parkinson disease (PD) are clinically manifested. It is currently accepted that metabolic alterations such as reduced Glu metabolism in the brain of these patients begins decades before the onset of disease symptomatology. Interestingly, at early stages of AD the metabolism of KB is not altered [30] suggesting that they may constitute an alternative fuel in the brain of AD patients during hypoglycemia [31]. In summary, both Glu and KB are key substrates in the enzymatic machineries involved in the biosynthetic cascades -primarily of lipids, but also of proteins and nucleic acids- that ensure neuronal and glial cell proliferation, myelin biogenesis, and reorganization of brain connectivity.

Bioenergetic failure impacts on synaptic transmission, myelinization, and plasma membrane biosynthesis leading to neurodevelopmental disorders in the newborn and to neurodegenerative disorders in the adult. Glu and ketones undergo glycolysis and ketolysis respectively and through the provision of pyruvate and acetyl-coenzyme A (acetyl-CoA) to mitochondria they are incorporated into the tricarboxylic cycle, providing the necessary energy for neurotransmitter (acetylcholine, glutamate and γ-aminobutyric acid (GABA)) and lipid (cholesterol, fatty acids, phospholipids and sphingolipids) synthesis. Cholesterol is the end product of the mevalonate pathway. Astrocytes provide neurons with this sterol through the Bloch pathway (Fig. 1). In addition to their key roles as structural components of the cell and the various membrane compartments, lipids play an important role in the regulation of the protein machinery that controls spine plasticity. Lipids undergo modifications necessary to dynamically change dendritic spine number, size and shape and thus indirectly contribute to determine the strength of synaptic transmission, which ultimately provides the substratum for memory and learning processes to take place [32–35]. When lipid metabolism fails to adapt to these dynamic challenges, correct dendritic maturation fails, with an inherent negative impact on neuronal function and circuit establishment. Thus, through the control

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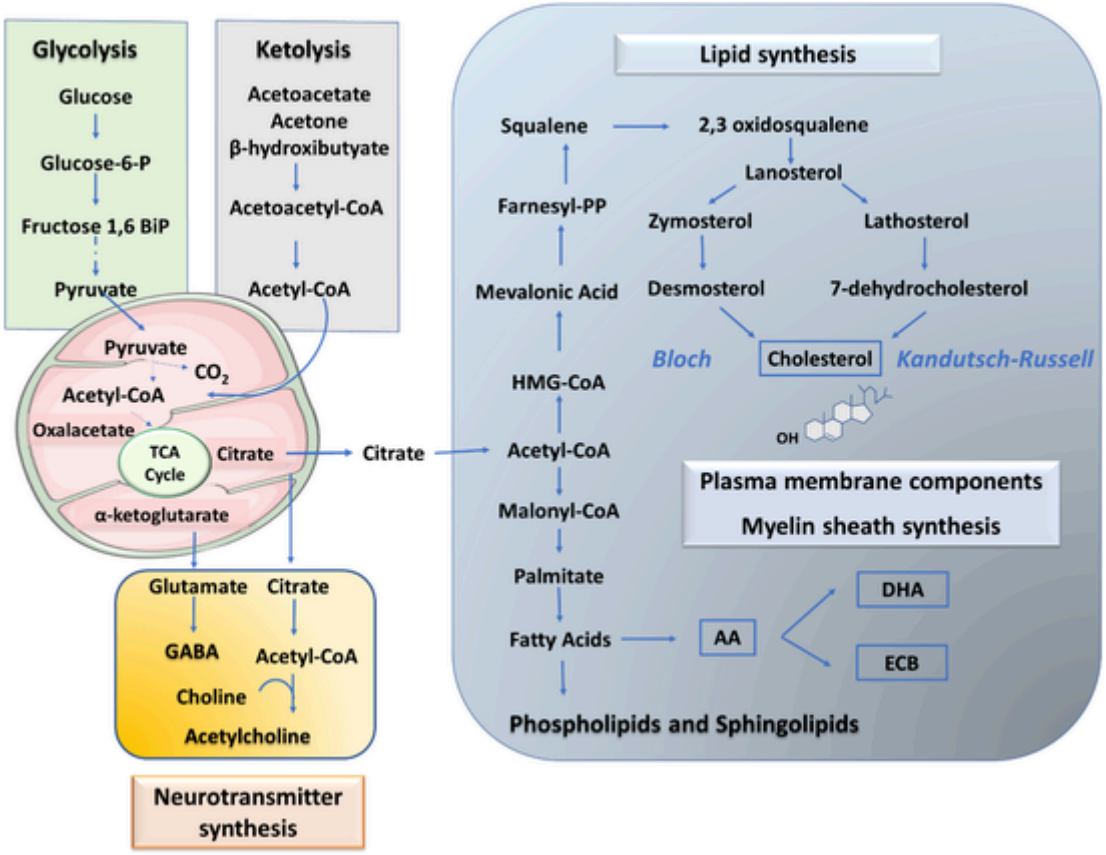

Fig. 1. Maintenance of brain homeostasis requires adequate energy provision.

of spine architecture, membrane lipids are fundamental players in synaptic structure and function.

We will next describe the importance of lipids, with special emphasis on cholesterol, docosahexaenoic acid (DHA), sphingolipids, endocannabinoids (ECB) and plasmalogens (Pls) at the dendritic spine level, how these lipids contribute to orchestrate synaptic transmission and how they regulate key physiological processes underlying brain development and pathology.

3. Cholesterol and cholesterol-enriched nanodomains

Cholesterol is involved in several important functions in the central nervous system (CNS). It is needed for the synthesis of axonal myelin sheaths and constitutes a key building block of the plasma membrane of all cellular constituents in the nervous system. Cholesterol levels in brain are finely monitored and regulated. Oligodendrocytes produce cholesterol to form the myelin sheath, while astrocytes produce cholesterol in the form of a cholesterol-apolipoprotein E (ApoE) complex to supply the neutral lipid to neurons [36,37] (Fig. 2). The availability of cholesterol in oligodendrocytes has been suggested to be a limiting factor for brain maturation, myelination, and neurotransmission [37]. The importance of this sterol for the brain is highlighted by the fact that this organ has the highest concentration of cholesterol (23 % of the body's cholesterol content) [38]. Neurons produce cholesterol until birth; in postnatal life, the cholesterol in brain is produced by oligodendrocytes and astrocytes [36,39].

Brain cells must regulate their own cholesterol levels since the BBB precludes the entry of lipoproteins that act as cholesterol carriers into the brain parenchyma [38]. Thus, altered cholesterol homeostasis can perturb CNS development and function and lead to neurological disorders [40–45]. If cholesterol in the brain exceeds the required level, it is transformed into 24-S hydroxycholesterol (24-OHChol) by the 24-hydroxylase (CYP46) and can cross the BBB to exit the brain (Fig. 2). Alternatively, cholesterol can exit the brain through other metabolites such as 5α-hydroxy-6-oxocholesterol (3β,5α-dihydroxycholestan-6-one), 7β-hydroxycholesterol, and 7-oxocholesterol, considered to be formed through reactive oxygen species [46]. It has been suggested that some brain regions may be more sensitive to cholesterol levels than others since CYP46 is not uniformly distributed but occurs in specific brain areas [47,48].

Cholesterol concentration is a major modulator of the physical properties of the bulk membrane, e.g. promoting the formation of lateral heterogeneities such as liquid-ordered (Lo) domains ("lipid rafts") [49], which exhibit higher rigidity and thickness than those of the rest of the membrane bilayer. By forming these membrane nanodomains, cholesterol together with sphingolipids compartmentalize the plane of the membrane and the spatio-temporal processes that occur in this area [50], of great importance at dendritic spines [51]. Lipid nanodomains at dendritic spines recruit and associate with postsynaptic proteins, e.g., neurotransmitter receptors [51–53]. Indeed, cholesterol depletion and enrichment have both been reported to impact on the function of the nicotinic acetylcholine receptor [54,55], the *N*-methyl-D-aspartate (NMDA) receptor [56], the glycine receptor [57], and the subtype-1A [58] and subtype-7 serotonin receptors [59].

Lipid nanodomains also facilitate the recruitment of proteins with affinity for certain lipid constituents of these domains and allow the formation of protein-protein complexes that activate specific signaling pathways [60]. The postsynaptic density protein 95 (PSD-95) and the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) are typical examples of heterologous protein complexes between scaffolding protein-neurotransmitter receptors associated with lipid nanodomains [61–64]. Cholesterol has been defined as the core component of dendritic spines [9]. Its removal from membranes triggers the gradual loss of synapses (both inhibitory and excitatory) and the elimi-

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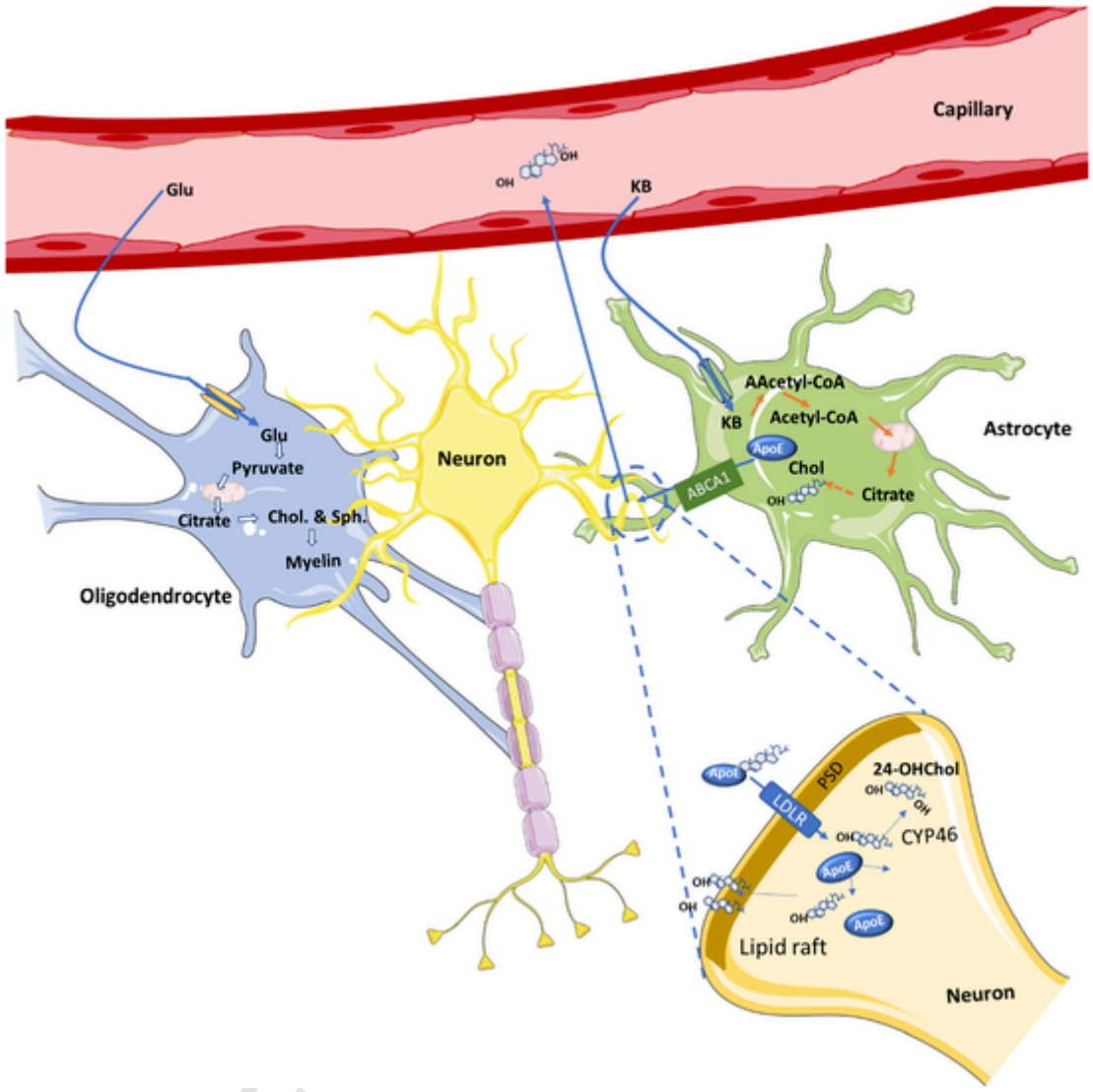

Fig. 2. Cholesterol synthesis by oligodendrocytes and astrocytes in brain. Cholesterol biosynthesized by both oligodendrocytes and astrocytes is a substrate to produce axonal myelin sheaths, in turn necessary for neurons to support fast nerve transmission. Glu and ketones are the energy-rich substrates for pyruvate production; the former is imported to oligodendrocytes and astrocytes through Glu transporters (Glut1). Glu and KB generate pyruvate, acetyl-CoA, citrate and finally cholesterol (Chol) and sphingolipids (Sph), both necessary for myelin synthesis. Astrocytes deliver cholesterol to neurons in the form of a cholesterol-ApoE complex. Cholesterol can exit the brain as 24-S hydroxycholesterol (24-OHChol). ATP-Binding cassette transporter A1 (ABCA1), low density lipoproteins receptor (LDLR), 24-hydroxylase (CYP46). Figure created using Servier Medical Art Commons Attribution 3.0 Unported License (http://smart.servier.com). Servier Medical Art by Servier is licensed under a Creative Commons Attribution 3.0 Unported License.

nation of dendritic spines [63,65,66]. Cholesterol-rich lipid nanodomains dynamically crosstalk with the actin cytoskeleton subjacent to the cytoplasmic leaflet of the plasma membrane [63,67,68]. Through this interaction, filamentous actin (f-actin) actively participates in the regulation of spine size and synaptic efficacy. High-frequency stimulation induces LTP, promoting the polymerization of actin and ensuing remodeling and enlargement of spines [69,70], while low frequency stimulation promotes LTD, causing loss of f-actin and dendritic spine shrinkage [70,71]. For a review on the relationship between LTP and actin see ref. [72].

The differentiation and maturation of the dendritic spine is finely regulated by proteins that are organized in nanoclusters both at pre- and post-synaptic sites. An example of such organization is provided by the tetraspanin superfamily of proteins (TSPANs), organized in membrane lipid domains enriched in cholesterol [73]. TSPAN5, a member of this superfamily, is a cholesterol-binding protein that localizes postsynaptically in pyramidal excitatory neurons. By promoting the clustering at the spine surface of another protein, neuroligin-1, TSPAN5 interacts with presynaptic neurexins and controls spine maturation [74]. In agreement with these observations, TSPAN5 knockout mice have a reduced number of spines [74]. 24-OH-Chol, the most abundant cholesterol metabolite in brain, has also been found to modulate LTP by acting on NMDA receptors [75]. This is clear from the examples in this section that cholesterol is an essential structural and functional component of synapses and an important modulator of neurotransmission and synaptic plasticity.

3.1. Synaptopathies associated with dysregulated cholesterol metabolism

The dysregulation of cholesterol metabolism in the CNS is considered to be a causative factor of several major brain disorders [76]. In the process of aging, membrane cholesterol diminishes; this decline has been reported to occur concomitantly with the cognitive deficits that become apparent at this stage of life [77,78]. Abnormal cholesterol metabolism plays a crucial role in the development of neurological disorders such as AD, PD, Huntington disease (HD), Niemann-Pick type C

disease, and schizophrenia spectrum disorders. AD is one of the most common aging-related diseases of the CNS. High levels of circulating cholesterol, mainly in mid-age, are associated with increased risk of developing AD [79]. Additionally, inheritance of the ε4 allele of the apolipoprotein E (*APOE*), the principal cholesterol transport protein in brain, constitutes a major risk factor for the disease [80]. Also linked to the pathophysiology of AD is carrying the polymorphisms of cholesterol 24-hydroxylase, the ATP-binding cassette transporter A1 (ABCA1), and lipoprotein receptor-related protein [81–84]. In AD, cholesterol has been reported to accumulate in areas of amyloid plaque deposition and abnormal neurites. There is evidence suggesting that cholesterol is involved in amyloid precursor protein (APP) metabolism [85], in the susceptibility of neurons to Aβ toxicity, and in the progression of tau pathology [86,87]. However, the mechanisms underlying the link between altered cholesterol metabolism and the above-mentioned pathological scenarios are not fully understood and constitute an area of active research in AD.

PD is the second most prevalent age-related progressive neurodegenerative disorder. Its pathology involves the accumulation of α-synuclein and formation of Lewy bodies (LB) with the loss of dopaminergic neurons in the substantia nigra [88]. Men have a higher risk than women of developing PD [89]. Elevated levels of both cholesterol and oxysterol contribute to the development of PD by α-synuclein aggregation [90]. Carrying the APOE ε2 allele has been associated with lower low-density lipoprotein cholesterol (LDL-C) [91] and with a higher prevalence of PD [92]. Interestingly, higher serum LDL-C has shown protection against the risk of PD [93].

HD is also associated with alterations in cellular cholesterol metabolism. HD results from polyglutamine expansion in the huntingtin protein [94] and is characterized by the degeneration of neurons of cerebral cortex and striatum [95]. Lower plasma cholesterol levels, reduced brain cholesterol synthesis, and cholesterol accumulation in neuronal plasma membranes have been observed in patients with HD and in animal models of the disease [96].

Niemann-Pick type C disease is a rare progressive genetic disorder characterized by altered and dysregulated cholesterol biosynthesis and intracellular trafficking. Consequently, cholesterol and other lipids are abnormally accumulated in late endosomes/lysosomes within various tissues of the body, including the brain [97]. Further research will help shed light on how the alteration of cholesterol metabolism impacts on the neuropathology of this cholesterol metabolic disorder.

Schizophrenia spectrum disorders are another complex series of serious mental disabilities that have been associated with lipid alterations. Schizophrenic patients have reduced HDL cholesterol in comparison with healthy individuals [98]. In a double-blind study of patients with schizophrenia spectrum disorders a strong association was reported between cholesterol levels and cognition [99].

3.2. Polyunsaturated fatty acids

Polyunsaturated fatty acids (PUFAs) are recognized as important biomolecules that contribute to the regulation of membrane biophysical properties [100]. PUFAs contribute to the adjustment of the number of dendritic spines and hence the number of functional synapses [101]. In addition, PUFAs are the precursors for the biosynthesis of lipid mediators with pro-inflammatory (AA derivatives), anti-inflammatory (DHA metabolites) or neuromodulatory effects (endocannabinoids) [31]. Docosahexaenoic acid (omega 3, n-3, 22:6; DHA) is a very important PUFA. It is synthesized from the essential fatty acid α-linolenic acid (n-3, 18:3, ALA). It not only contributes to the structural requirements of the membrane (e.g., increasing the fluidity of the bilayer) but also participates in cell signaling and intercellular communication mechanisms, gene expression, and production of lipid mediators. The brain and eye have higher DHA contents than other organs, amounting to 18 % of the total fatty acid content in adult human brain gray matter [102] and 8 % in infant cerebral cortex [103]. Reduced DHA content is linked to poorer cognitive development [104]. Appropriate levels of DHA during fetal life and infancy are essential to ensure normal development. In adults, the conversion of ALA to DHA is more efficiently carried out in women than in men [105,106]. One possible explanation for this metabolic difference is that women require higher amounts of DHA during pregnancy and lactation. Indeed, the amount of DHA in the brain increases 35-fold from week 30 of gestation to 18 months of age [29,107]. The last trimester of pregnancy is the most active period of brain cell division and therefore an adequate supply of DHA to brain cells is critical for normal growth, neurological and visual development and function, and learning behavior [108]. Another plausible explanation for this sexual dimorphism has been recently postulated by Metherel and collaborators [109]. These authors suggest that females have higher blood DHA levels than males due to higher DHA synthetic rates and/or a longer half-life of the fatty acid. Previous reports by Giltay and coworkers support the notion that higher DHA concentrations found in women are the result of estrogenic effects that end up inducing DHA synthesis from plant precursors [110].

DHA influences membrane order because of its highly unsaturated nature, impacting on the cell membrane responsiveness to either electrical or chemical signals. In neuronal cell cultures the addition of DHA enhances spontaneous glutamatergic synaptic activity, promotes NMDAR function, and increases the levels of AMPAR and NMDAR subunits [111,112].

In rodents, maternal dietary deprivation of DHA precludes induction of LTP [112]. In older rats the supplementation with DHA restores LTP impairment [113]. While DHA deficiency affects spatial learning, high DHA levels improve it [114,115], highlighting the importance of synaptic membrane composition for neuronal function.

Prenatal stress has been shown to negatively impact on learning and memory, enhancing oxidative mitochondrial DNA damage with changes in mitochondrial complexes I-V and in mitochondrial fusion/fission processes [116,117]. DHA has protective effects over prenatal stress and ameliorates these changes [116]. In the hippocampus of n-3 fatty acid deficient mice, decreased levels of the postsynaptic scaffold proteins PSD-95 and cofilin has been reported [118]. In agreement with this observation, loss of PSD-95 is inversely correlated with DHA dietary supply in a mouse model of AD [119].

In humans, preterm infants have lower brain DHA levels than term infants [119,120] and the level of n-3 PUFAs in erythrocytes, also recognized as the n-3 PUFA index, is considered as a biomarker for several neurodevelopment diseases such as autism spectrum disorder [121], attention deficit hyperactivity disorder (ADHD) [122] and schizophrenia spectrum disorders [123]. Additionally, in patients diagnosed with autism or attention deficit hyperactivity disorder, abnormally low DHA levels have been reported in several brain regions [124].

As a response to n-3 PUFA deficiency, brain DHA is replaced by docosapentaenoic acid (DPA n-6) [119]. This single double-bond replacement of DHA by DPA in the membrane causes a more even distribution of chain densities along the bilayer that has been suggested to influence the function of integral membrane proteins [125] and could contribute to both behavioral and functional abnormalities described for rodents with dietary n-3 PUFA deprivation [126,127].

The molecular mechanisms that have been proposed in relation to the neurobehavioral effects of DHA include an increase in cell membrane fluidity [128], the promotion of neurite extension [129,130], the inhibition of apoptosis [131,132], enhanced synthesis of the phosphatides in synaptic membranes [133], and an increment in the number of dendritic spines and thus the number of functional synapses [101].

DHA has also been shown to prevent dendritic spine loss in hippocampal CA1 pyramidal neurons exposed to inflammatory agents [134]. More recently, inhibition of DHA release from the membrane was shown to significantly reduce dendritic spine density and excitatory synaptic transmission [135]. In cell cultured neurons, DHA in-

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creased the density and size of synapses in a dose-dependent manner [136].

3.2.1. Synaptopathies associated with dysregulated DHA metabolism

Epidemiological and animal studies indicate that consumption of DHA is associated with reduced incidence of AD-like brain pathology [137,138]. DHA is indeed reduced in the brains of patients with AD [139,140], and significant reductions in the degree of unsaturation and peroxidability indexes are observed in this disease as compared to healthy controls [141]. These lipid alterations are observed early in AD pathogenesis, particularly in the frontal and entorhinal cortices [142]. It is worth mentioning that the hippocampus is the region of the brain where DHA levels are more significantly reduced in AD patients [31]. More recently, DHA was reported to have anti-aggregation properties, preventing both Aβ40 and Aβ42 fibrillogenesis [143]. These authors suggested that DHA is capable of directly interacting with both Aβ40 and Aβ42 peptides, exerting beneficial effects on AD.

Other benefits of DHA in relation to brain pathologies include increasing cerebral blood flow, decreasing Aβ deposition and tau phosphorylation, reducing activities of β- and γ-secretase, enhancing APP cleavage by α-secretase, increasing dendritic spine densities and restoring synaptic function in the hippocampus [134,144,145]. In vitro studies performed on human embryonic kidney (HEK) cells stably transfected with amyloid precursor protein (the HEK-APP clonal cell line), showed that DHA supplementation significantly increased membrane fluidity and shifted the processing of APP towards an enhanced secretion of non-amyloidogenic soluble amyloid precursor protein (sAPPa). These positive changes correlated with substantial protection against mitochondrial dysfunction and apoptosis [146]. These data agree with the growing evidence that DHA favorably impacts on membrane phospholipid composition and function.

Significantly reduced levels of DHA have been found in samples of detergent-insoluble membrane fractions (the biochemical counterpart of lipid rafts) obtained from the frontal cortex of postmortem brains of patients with early motor stage PD and incidental PD [147]. Reduced levels of DHA were found in fatty acid profile analytes of temporal cortex lipid extracts obtained from a non-human primate model of parkinsonism that received levodopa treatment [148]. In agreement with these findings, mice that received a diet rich in DHA and subsequently received the toxin-induced neuronal degeneration 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) treatment [149,150] demonstrated the beneficial effects of dietary omega-3 PUFAs [151]. MPTP can cross the BBB and produces a Parkinsonian syndrome resembling the actual PD, presumably by inhibiting complex I of the mitochondrial electron-transport chain, leading to energy failure and cell death. DHA has been reported to reduce the severity of or delay the development of levodopa-induced dyskinesias in a non-human primate model of PD [152]. Low DHA levels were also reported in detergent-resistant membrane fractions obtained from LB [153]. However, the α-synuclein neuropathology was reported to be enhanced by DHA in a mouse model of PD [154], in agreement with findings of Sharon and coworkers who also found increased amounts of DHA in PD and LB brains [155]. Further research is therefore required to resolve these contrasting results and establish whether a diet high or low in DHA provides neuroprotective effects in PD.

The putative benefits of DHA as a regulator of neurodegeneration in HD should also be further explored, since the benefits of consuming DHA-enriched diets have only dealt with effects on the cardiovascular comorbidities experienced by HD patients but not on potential benefits for the CNS [156,157].

A recent study evaluated the differential abundance of multiple lipid species in the liver of an animal model of Niemann-Pick disease 1 (Npc1−/−) [158]. After being synthesized in the liver, free fatty acids (FFA) circulate to be imported into other tissues, including brain, by fatty acid transport proteins. These authors reported the altered expression of fatty acid transport proteins in both the liver and brain tissue of Npc1−/− mice. Pergande et al. suggest that FFA, including DHA, fail to reach their destination and thus exhibit a pathological distribution. This in turn contributes to the neurodegeneration phenotype found in NPC1 [158].

Recent data indicates that patients with schizophrenia spectrum disorders have a deficiency in n-3 fatty acids, including DHA, in their phospholipids [159,160]. Supplementation with n-3 fatty acids has been reported to provide beneficial effects to schizophrenic patients and in particular women with psychotic-like symptoms [160–162].

3.3. Endocannabinoids

The endocannabinoid (ECB) system is present in almost every mammalian organ and tissue. It comprises a family of lipid second messengers and proteins that regulate their own synthesis and deactivation [163]. In brain, ECBs combine with the canonical cannabinoid receptors (CB1 and CB2 receptors) on synaptic terminals and regulate ion channel activity and neurotransmitter release. Additionally, cannabinoids can interact with a non-canonical signaling network by modulating ionotropic cannabinoid receptors (TRP channels) and other GPCRs (GPR55, PPARα) [164]. Through this modulation of synaptic efficacy they have an important role in many brain processes including memory, anxiety and movement [165,166]. The CB1 receptor is the most abundant G-protein-coupled receptor in mammalian brain [167]. Neuronal CB1 receptor is preferentially expressed at presynaptic sites, but also present at postsynaptic sites (somatic and dendritic localization) [50,168,169]. In addition to its plasma membrane localization, the CB1 receptor has also been identified at the inner membrane leaflet of neuronal (approximately 15 % of total cell CB1 receptors) and skeletal muscle cells, where it controls cellular respiration and energy production [170–172]. Neurotransmitter release is a very energy-demanding process [173], and mitochondria can modulate its efficiency by different means [174]. Activation of mitochondrial CB1 receptors hinders mitochondrial respiration, thereby altering the energy supply (ATP) necessary for the release of neurotransmitters at presynaptic sites [173,174], with detrimental effects on synaptic plasticity.

During the perinatal period, high densities of CB1 receptors are observed in fiber-enriched areas that are essentially absent from adult brain, suggesting a specific role of the endocannabinoid system in neural development [175]. Indeed, during early phases of neuronal development the ECB system mediates key functions such as axonal growth, fasciculation, and the establishment of correct neuronal connectivity [176–178]. All of these have been suggested to be essential for guidance processes that result in the establishment of key cortical–subcortical connections [179–181], for instance. After birth and towards young adulthood the CB1 receptor expression pattern increases significantly in the frontal cortex, striatum and hippocampus [179]. These changes in the levels of expression of CB1 receptor may account for negative effects of cannabinoid consumption in adolescence and children born to women who consumed marijuana during pregnancy [182]. Cannabis causes cognitive, motor and social deficits that last into the adulthood of the offspring [176].

In an animal model of neonatal stress related to maternal deprivation, animals showed an increased level of the ECB 2-arachidonoylglycerol (2-AG), a decrease in hippocampal CB1 receptor immunoreactivity and hippocampal monoacylglycerol lipase, the enzyme involved in the degradation of this ECB [175]. These alterations show gender differences since they are more marked in males than in females [175,183]. These observations were obtained using a stress animal model that has contributed to the understanding of how the endocannabinoid system is a key target of epigenetic factors and extremely critical during developmental periods. All in all, the ECB signaling system can modulate synaptic plasticity through activation and inhibition

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of a plethora of mechanisms, providing further complexity to the pathophysiological consequences of ECB system dysregulation.

It is worth noting that CB1 and CB2 receptors and ECBs are also influenced by the cholesterol composition of the cell membrane [184]. The CB1 receptor has a specific cholesterol binding site [185] and the activity of CB1 receptor in nerve cells is negatively modulated by cholesterol [186]. Cholesterol is able to increase the basal activation levels of the CB2 receptor by exerting allosteric effects on an intracellular domain of the protein [184]. Another important ECB, anandamide, has selectivity for cholesterol and ceramide-rich membranes. Di Scala and coworkers have proposed that cholesterol may regulate the entry and exit of anandamide in and out of CB1 receptor by interacting with low affinity cholesterol recognition sites (CARC and CRAC) located at the inner leaflet of the plasma membrane [187]. Upon binding to ceramide, the degradation pathway of both lipids is turned into action [187].

Activation of postsynaptic excitatory neurotransmitter receptors (e.g., nicotinic acetylcholine receptors (nAChRs) and glutamate receptors) causes LTP due to the depolarization of the dendritic spine through Ca^{2+} influx and activation of a Gq-protein. In turn, Gq protein stimulates ECB synthesis through activation of phospholipases C and D that hydrolyze plasma membrane phospholipids [188,189]. The newly synthesized ECBs are released into the synaptic cleft and activate ECB receptors at the presynaptic neuron. This retrograde signal regulates synaptic transmission by attenuating presynaptic depolarization and subsequent neurotransmitter release [190].

CB1 receptors at dendritic spines colocalize with the PSD scaffold protein PSD-95 [169]. Activation of postsynaptic CB1 receptors can structurally remodel dendritic spines by regulating the activity levels of WAVE1 [169]. Activation of postsynaptic CB1 receptors of mature cortical neurons limits the conversion of G-actin to f-actin, leading to a reduction in bouton size of spines and thus causing depletion of the classical mushroom-shaped morphology observed in mature spines.

The transient receptor potential vanilloid type-1 (TRPV1) channels are expressed both pre- and post-synaptically, contributing to the regulation of synaptic strength [191–193]. TRPV1 can be activated by a plethora of molecules including cannabinoids [194]. Although TRPV1 favors pain transmission and neurogenic inflammation [195–198], it also contributes to a rise in intracellular Ca^{2+} that activates calmodulin and calcineurin, two intracellular proteins that either stabilize the channel in a closed conformation, or dephosphorylate it, resulting in its inactivation [197,199–201]. Desensitization of TRPV1 has been suggested to contribute to the analgesic, anti-inflammatory and anticonvulsant effects of TRPV1 agonists [69,83,84]. In addition, TRPV1 channels in CNS neurons have been suggested to exert effects opposite to those induced by canonical CB1 receptors [202–204].

GPR55 also belongs to the family of GPCRs and has been reported to be activated by low concentrations of AN and 2-AG [205,206]. Furthermore, GPR55 and CB1 receptors have been shown to be able to form heteromers [207,208]. As with TRPV1, it has been suggested that activation of GPR55 plays an opposite role to CB1 receptors, inducing neurotransmitter release [209].

3.3.1. Synaptopathies associated with dysregulation of the endocannabinoid system

The ECS is critical at neurodevelopmental stages and hence disturbances either caused by early life stressful events or cannabis consumption can lead to important neuropsychiatric pathologies [175]. In animal models and human studies, the ECB system has been shown to contribute to the neurologic deficits present in many neurodegenerative diseases, including AD, PD, HD and schizophrenia spectrum disorders [210–212]. Dysregulation of the ECS may be associated with some forms of epilepsy [213–219]. Epilepsies are caused by defects in membrane excitability that lead to aberrant synchronization of neural networks. The ECS has been reported to have a neuroprotective role in epilepsy. Marsicano and colleagues postulated that the ECS plays an important role in this disorder, counteracting epileptiform discharges [213,216] via the increase of ECB release during epileptic seizures. They postulated that ECBs stimulate pre-synaptic CB1 receptors, thus reducing glutamate signaling that in turn inhibits epileptic seizures [213,216]. Supporting data shows that exogenous CB1 agonists or selective MAGL or FAAH inhibitors also protect neurons from seizures [233,234]. However, Ludányi and colleagues reported increased excitability and neuronal damage in epileptic patients that presented both reduced 2-AG levels and CB1 receptor expression in glutamatergic axon terminals, whereas the expression of CB1 receptors in GABAergic neurons was unaffected [235]. Pre-synaptic inhibition of GABAergic terminals may also contribute to lowering the threshold of neuronal excitability in these patients [236].

The TRPV1 channel has been reported to facilitate epileptogenesis in patients affected by mesial temporal lobe epilepsy [237]. TRPV1 has an important role in the induction of seizures. Supporting evidence shows that prolonged or repeated stimulation of the TRPV1 channel induces rapid dephosphorylation (desensitized) and reduced neuronal activity [238]. Considering that both CB1 and TRPV1 receptors coexist in several brain structures, such as the hippocampus, and that both can be activated by endocannabinoids and produce opposite effects on neuronal excitability, their activation must be finely tuned. The plasma membrane plays a major role in the compartmentalization of these signaling pathways.

Antiepileptic and anti-convulsive effects via direct activation of PPAR-α receptors have also been described [239,240], contributing to the neuroprotective effects through a PPAR-α-mediated mechanisms [241].

AD patients have lower expression of CB1 receptors. This deficit shows correlation with hypophagia but not with other AD molecular markers or cognitive status [220,221]. Reduced expression of CB1 receptors has been described in areas of microglial activation [221]. In contrast, CB2 receptor levels are augmented in AD patients, showing correlation with increased Aβ-42 levels but not with cognitive status [220].

The ECB system has been involved in the pathophysiology of parkinsonism and MPTP-lesioned, non-human primate models of PD [222]. In rat models of PD anandamide levels are elevated [223,224]. In line with these findings, increased levels of ECB are found in the cerebrospinal fluid of PD patients [225]. Clinical studies are still controversial and inconclusive [226] with respect to the ability of cannabis-based therapies to improve the motor problems in PD patients.

Massive loss of CB1 receptors has been reported in various basal ganglia structures in Huntington disease patients [227]. Several studies performed using animal models of HD also suggest that the ECB system is dysregulated in different brain regions [210]. In late-onset HD, the loss of CB1 receptors is accompanied by enhanced expression of CB2 receptors [228,229].

In a mouse model of Niemann-Pick disease type C, Oddi and coworkers [230] found a robust alteration of distinct components of the ECB system in various brain regions. Their data suggest that dysfunctional ECB signaling contributes to worsening of the neurological symptoms of this disorder. More recently, the inhibition of the fatty acid amide hydrolase enzyme was shown to reduce sphingomyelin and cholesterol levels in Niemann-Pick type C patient-derived cells as well as in in the brain of a mouse model of this disease [231], demonstrating a pathophysiological crosstalk between neuronal sphingomyelin, cholesterol and the ECB system.

The risk of developing schizophrenia disorders and the worsening of symptoms of the illness is higher in frequent cannabis users [211,212]. Higher metabolism of 2-AG, in parallel with greater CB1 receptor binding and lower levels of CB1 receptor mRNA and CB1 receptor protein has been described in the prefrontal cortex of subjects with schizophrenia spectrum disorders. Certainly, the long-lasting deleterious effects of synthetic cannabinoids on cognitive function in schizophrenic patients

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appears to be enhanced when exposure occurs during periods of intense neural circuitry development, such as adolescence. The prefrontal cortex mediates higher cognitive functions and emotional regulation and undergoes significant maturation during adolescence. This explains why exposure to cannabinoids (e.g. Δ^9-tetrahydrocannabinol (THC), a psychoactive component of cannabis) during this period of life disrupts the normal developmental process by inducing premature pruning of dendritic spines and allostatic atrophy of dendritic arborization in early adulthood [232].

3.4. Sphingolipids

Sphingolipids are ubiquitous constituents of plasma membranes, regulate numerous cellular processes, and are also important signaling molecules [242]. Their saturated acyl chains allow this class of lipids to pack against one of the faces of cholesterol [243], thus favoring the formation of liquid-ordered domains that are distinct from the bulk liquid-disordered phase of the plasma membrane [244]. By contributing to the formation of specialized micro/nanodomains or lipid rafts, sphingolipids regulate cellular signaling through the interaction with proteins and by providing unique physical properties to the plasma membrane. The plasma membrane of brain cells is rich in sphingolipids. Ceramide and sphingosine are considered two important sphingolipid regulators of synaptic functions. They participate in synapse formation, neurotransmitter release, and synaptic plasticity [76,243,245]. Sphingolipids at presynaptic sites modulate synaptic transmission by facilitating SNARE complex assembly and activating synaptic vesicle exocytosis [246]. They regulate the postsynaptic excitatory currents, e.g. by controlling the clustering and membrane insertion of NMDA receptors [247]. Sphingolipids regulate the trafficking and expression of transmembrane receptors; for example, their deprivation negatively impacts on for instance the postsynaptic localization of the nAChR at the cell surface [248]. Disturbance of liquid-ordered lipid microdomains by simultaneous cholesterol removal and hydrolysis of sphingomyelin into ceramide increases the rate of recovery from desensitization and agonist affinity of the neuronal α7 nAChR in rat hippocampal neurons; in contrast, desensitization half-time decreases in the case of the α3β2 nAChR [249].

Sphingomyelins in spine membranes interact with the actin cytoskeleton by modulating Rho GTPases and the size of spines. When sphingomyelin levels are high, they diminish the activity of RhoA GTPase, along with the inhibition of its effectors ROCK and Profilin IIa; these changes are paralleled by reduced levels of f-actin and diminution of spine size [250]. In contrast, when sphingomyelin levels are low, elevated activity of the RhoA-ROCK-Profilin I pathway augments actin polymerization and spine size [251]. Hence, the maintenance of adequate sphingomyelin levels is necessary for the membrane morphological and functional modifications that take place during synaptic plasticity.

Another major sphingolipid, ceramide, promotes spine maturation via its involvement in the transformation of "immature" dendritic filopodia into mature spines [252]. Ceramides also regulate spine plasticity by controlling receptor clustering and thus by modulating excitatory postsynaptic currents, as is the case with NMDA receptor [247]. Indeed NMDA receptors can be induced to traffic to or from raft lipid-ordered domains, a redistribution involving transient modifications in the level of diacylglycerol and ceramides that have important implications for signal transduction, synaptic plasticity, and cell survival [253,254].

Gangliosides are mono- or multi-sialosylated glycosphingolipids that are highly abundant in the nervous system [255]. Their importance resides in the fact that they correlate with several neurodevelopmental milestones such as neural tube formation, neuronal differentiation, axon genesis, outgrowth of dendrites and synaptogenesis [245]. In addition, ganglioside synthesis enhances ATP-induced LTP in hippocampal CA1 neurons, a phenomenon that can be blocked by NMDA antagonists [256]. In agreement with these observations, exogenous GQ1b has been reported to increase BDNF through regulation of the NMDA receptor in rat cortical neurons [257].

Sphingolipid profiles undergo dynamic changes as the brain develops and ages, further indicating their involvement in differentiation processes and in the maintenance of neuronal functions [245,258].

3.4.1. Synaptopathies associated with dysregulated sphingolipid metabolism

Sphingolipids have been involved in several neurological diseases [20]. Dysregulated sphingolipid metabolism plays important roles in the pathogenesis of a vast number of neurodegenerative conditions [254]. Indeed, AD is accompanied by deregulated sphingolipid metabolism: brain cell membranes are enriched in sphingomyelins and reduction in their levels leads to elimination of dendritic spines [63] that may precede by decades the symptomatic stages of the disease.

Ceramide levels are elevated in the human brain of patients with AD and this sphingolipid has been proposed to be a predictive serum biomarker [259]. Treatment with fibrillar amyloid β was reported to induce N-SMase expression and increase ceramide production in human neurons in primary cultures [260]. In accordance with this observation, the knockdown of N-SMase was reported to reduce the cell death associated with the amyloid β treatment in this animal model, suggesting an active role of N-SMase in AD [261]. Sphingomyelin has also been reported to promote aggregation of amyloid β and a sphingomyelin binding motif has been identified in amyloid β [262,263].

Increased ceramide content has been observed along aging [264]. This age-related increase results in an abnormal ratio of ceramide to other sphingolipids that has been suggested to play a role in cognitive decline as well as in altered nerve conduction and loss of synapses [63], endosomal/lysosomal abnormalities [265], and a higher vulnerability to oxidative damage [266–269]. The aforementioned ceramide increases during aging have been associated with increased N-sphingomyelinase (N-SMase) activity [266,269]. Ceramide synthesis by N-SMase2 cleavage of sphingomyelin has been shown to support neurotransmitter release by promoting vesicular fusion [270], whereas sphingomyelin depletion has been associated with neurotransmitter receptor instability [63]. Decreased ceramide levels correlate with increased PSD-95 postsynaptic protein levels as well as increased numbers of AMPA receptors and altered subunit composition of NMDA receptors, changes that affect learning and memory [271].

There is also evidence pointing to the participation of gangliosides at the initiation and progression of AD [272,273]. The rationale behind this claim is that the rate-limiting step in the biosynthesis of gangliosides is catalyzed by the enzyme glucosylceramide synthase and deletion of its coding gene in subsets of adult forebrain neurons of 5× familial AD mice [274] significantly improves spatial memory and prevents the loss of dendritic spines in the hippocampal dentate gyrus [275]. Further research is needed to clarify the association between altered sphingolipid metabolism and AD.

Association between PD and lysosomal sphingolipid metabolism defects have been reported [276]. Aggregation of α-synuclein and the formation of LB, lipid-protein cellular inclusions that results in impaired neurotransmitter release and uptake are linked with PD. Some mutations found in PD patients are specifically related to the alteration of sphingolipid homeostasis. Ceramides have been found to be accumulated in postmortem PD brains and altered in the plasma of PD patients. The increase in ceramide content is specifically involved in LB formation and PD progression [276,277]. Sphingomyelins are also increased in postmortem PD brains [278–280]. Augmented transcription of the enzymes responsible for de novo sphingolipid synthesis are also observed in PD patients [279]. Other studies report that mutations in the glucocerebrosidase gene confer increased susceptibility on the development of PD [245] since reduced activity of the enzyme has been found in the brain of PD patients [281,282] and sustained systemic glucocere-

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brosidase inhibition induces brain α-synuclein aggregation in mice [283].

Profound alterations in the lipid composition of membrane microdomains isolated from the frontal cortex of patients with incidental PD have been reported. These patients have a high content of saturated lipids (16:0 and 18:0) and low content of unsaturated lipids that favor increased microdomain order [147]. In parallel with these findings, frontal cortex detergent-resistant membrane fractions from PD cortices presented a reduction in n-3 and n-6 long-chain PUFAs, especially DHA and AA. Also, lipid classes were found to be affected in lipid rafts of PD patients: increased levels of phosphatidylserine and phosphatidylinositol were reported while cerebrosides and sulfatides and Pls levels were diminished [147].

Defective sphingolipid metabolism plays an important role in the pathogenesis of HD [284–286]. Decreased levels of sphingosine-1-phosphate and increased levels of ceramides are present in animal models of this disease [284,287,288], which show affected de novo synthesis of sphingolipids right from the onset [286]. Indeed, ganglioside dysfunction in the corpus callosum appears to be an early event in HD animal models and it may potentially represent a critical molecular change influencing the pathogenesis of the disease [285].

The characteristic accumulation of cholesterol in Niemann-Pick disease is accompanied by the accrual of sphingolipids, but the mechanisms by which sphingolipids amass remain poorly understood [289]. The accumulation of sphingomyelin is common in Niemann-Pick disease variants type A, B and C, although defects in sphingomyelinase have only been identified in type A and type B, whereas the enzymic activity is normal in the disease [290]. Altered sphingomyelin levels have also been reported in a mouse model of Niemann-Pick disease type A that exhibits reduced spine number and size [250]. Sphingomyelin and glycosphingolipids accumulate in both animal models and in Niemann-Pick disease patients [291–293]. Promising diagnostic value has been attributed to sphingolipid analysis by mass spectrometry that can be applied to samples such as dried blood spots, plasma, or feces [294,295] from neonates at stages before the development of severe disease [295,296]. These advances may facilitate early intervention.

Disruption of sphingolipid metabolic pathway has also been associated with numerous neurological phenotypes [20]. To name some, ceramide synthetase 2 deficiency [297]; *trans*-2,3-enoyl-CoA reductase deficiency [298] and long-chain fatty acyl-CoA synthetase 4 (ACSL4) deficiency [299] clinically manifest as myoclonic epilepsy and non-syndromic intellectual disability, respectively. Deficiency in ceramide synthetase 1 is associated with both myoclonic epilepsy and intellectual disability. Deficiency in non-lysosomal glucosylceramidase and in fatty acid 2-hydroxylase deficiency has been reported in cerebellar ataxia, spastic paraplegia, and even intellectual disability [300]. For most of these disorders, no specific therapy is currently available; treatments are based on supportive management of the organs and systems involved.

3.5. Plasmalogens

Plasmalogens (Pls) are vinyl ether-bonded phospholipids [301]. They constitute the major subtype of glycerophospholipids in brain and nerve tissue [302–304]. Pls are enriched in PUFAs at the *sn*-2 position of the glycerol backbone. This property allows them to function as reservoirs of biologically active lipid mediators such as AA and DHA, that can be released upon hydrolysis.

Pls comprise two main types, ethanolamine Pls (Pls-Etn) and choline Pls (Pls-Cho) [16]. The brain is particularly enriched in Pls-Etn, which represent about 30 mol% of the total brain phospholipids [302], and about 70 % of all glycerophospholipids in myelin [305], whereas Pls-Cho are more abundant in heart and kidney [302]. In the brain Pls provide unique structural characteristics to biological membranes. Pls-Etn can modulate the membrane thickness and curvature [306]. Pls also facilitate signaling processes and have been recognized as powerful endogenous antioxidants since they can protect membrane lipids from oxidation [17]. Pls are of key importance in membrane dynamics and trafficking [307–310]. Furthermore, Pls are concentrated in specialized membranes such as myelin and synaptic vesicles. Thus, line with their proposed "fusogenic" properties, several authors have speculated about their roles in neurotransmission [311–313]. For instance, low levels of Pls can alter the biophysical properties of the cell membranes and this may in turn impair synaptic transmission as well as neurotransmitter release [307,314].

Pls are synthetized in peroxisomes. Defective synthesis of Pls leads to the Zellweger syndrome and Rhizomelic Chondrodysplasia Punctata. These fatal human diseases highlight the role of Pls in the development of bone, brain, lung, kidney, heart, and eye lens [16,315].

Homeostasis of Pls is associated with cholesterol synthesis [316] and Pls are necessary for the esterification of cholesterol [317]. A study using a mouse knock-out in an essential enzyme involved in Pls synthesis, dihydroxyacetone phosphate acyltransferase, demonstrated that several cholesterol-related processes were affected such as myelination, paranode organization, and Purkinje cell innervation [318]. Furthermore, cellular Pls levels have been suggested to regulate cholesterol synthesis by modulating squalene monooxygenase (SQLE) stability, an important enzyme in cholesterol biosynthesis [319–321] (see Fig. 1).

Honsho and coworkers [316] recently proposed that inhibition of SQLE by Pls-elevated levels efficiently reduces cholesterol synthesis. As previously stated, adequate cholesterol quantities are provided to neuronal cells mainly from glial cells [322]. Thus, Pls physiology must be highly regulated in astrocytes [323].

Another important role of Pls is their contribution to the organization of cholesterol-rich raft microdomains in the membrane [324,325] through which process they participate in cellular signaling [51]. Pls have been proposed to facilitate TrkB-signaling in lipid domains that induce brain-derived neurotrophic factor (*Bdnf)* expression. Increased *Bdnf* expression in the hippocampus has been reported in turn to promote neurogenesis associated with improvement of learning and memory in mice [326]. In contrast, low Pls levels in murine hippocampus have been associated with reduced learning and memory [326]. Low levels of Pls in the hippocampus have also been reported to induce neuroinflammation [327], and this in turn could contribute to the memory deficiency found in these rodents. Collectively, these data suggest that Pls are implicated in the regulation of memory-related gene expression in this area of the brain [326].

Furthermore, BDNF has been implicated in the regulation of adult neurogenesis, synaptic protein expression, dendritic spine maturation, and synaptic plasticity including LTP [328,329]. Finally, by recruiting the BDNF target receptor TrkB in membrane microdomains, Pls play a critical role in the induction of cellular signaling [330].

In terms of their antioxidant role, Pls have been referred to as "sacrificial oxidants" since their oxidative products have been shown to be unable to further propagate lipid peroxidation, thus terminating lipid oxidation [331]. Other studies highlight the preferential oxidation of the vinyl ether bond in Pls over double bonds found in other lipids of the plasma membrane [16,332].

Both in vitro and in vivo studies support the notion that Pls may stop microglia-mediated neuroinflammation [333–337] through the regulation of microglial cells to a less pro-inflammatory and to a more surveillance state [334,336,338].

A recent study by Gu and coworkers [301] reports that Pls contribute to the improvement of age-related cognitive decline through the promotion of neurogenesis. This effect appears to be mediated through synaptogenesis and synaptic vesicle formation that counteract the physiological and pathophysiological loss of synaptic connectivity and networking in aging and neurodegenerative process, respectively.

All in all, Pls are important players in cell membrane regulation, providing unique attributes to the membrane bilayer. Their singular

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chemical structure certainly contributes to this specificity, associated with the facilitation of specific signaling processes. They also play a role in protecting membrane lipids from oxidation. They further contribute to the prevention of memory loss and the reduction of neuroinflammation.

3.5.1. Synaptopathies associated with dysregulation of plasmalogens

Research on the emerging roles that Pls play in health and disease has increased in recent years [301,310,339]. Reduced levels of Pls-Etn have been reported to be associated with both aging [340] and several neurodegenerative diseases, including AD [341–344], PD [17, 344–346] and Niemann-Pick type C disease [347].

As we age there is a progressive decline in brain synaptic connectivity that results in cognitive impairment and may further lead to neurodegenerative disorders conducive to full states of dementia [348, 349]. Neuroinflammation and synaptic loss along with microglial dysfunction [350,351] accompany the aging process. In a natural aging rodent model, increasing Pls levels have been proposed to promote synaptic plasticity and neurogenesis, and to inhibit the age-related microglia-mediated neuroinflammation thus promising therapeutic benefits [301].

In AD patients Pls-Etn and Pls-Cho are reduced in affected brain regions that correlate with the severity of the disease [16,352,353]. Furthermore, Pls deficiency in AD has been directly correlated with the patient's clinical stage of dementia [302]. A decade ago, Kou et al. [354] reported that loss of Pls in the brain of AD patients was associated with peroxisome-related alterations. Not only were brain Pls in these and other AD patients lower, the levels of PUFAs such as DHA and AA were also low [353,354]. Thus, Pls deficiency, together with peroxisome dysfunction, may be a specific independent marker of AD pathology [355].

PD patients exhibit 20 % lower Pls concentrations in total plasma phospholipids compared to healthy individuals [17]. The lipid composition of lipid raft from postmortem human frontal cortex of PD patients showed diminished PUFA content, in particular of DHA and AA [147] as well lower brain Pls-Etn [345,346]. Miville-Godbout and coworkers further showed that administration of Pls precursors are effective for the provision of neuroprotection [346].

Using a mutant BALB/c mouse model Schedin and coworkers discovered that peroxisomal deficiencies occur long before the manifestation of Niemann Pick disease symptoms [347]. The only phospholipid change found in the brain of these rodents was a 33 % decrease in Pls-Etn, probably due to impaired peroxisomal synthesis rather than increased breakdown of Pls. The content of brain Pls-Etn in HD has not been reported to change [356]. Plasma Pls levels are reduced in schizophrenic patients, leading to the suggestion of impairments in membrane structure and function [357]. Speculations have also been made on whether this membrane lipid abnormality can influence presynaptic dopamine signaling [358]. However, Wood and collaborators reported that Pls in frontal cortex samples of postmortem schizophrenic patients are elevated and that this structural alteration of membrane glycerophospholipids may be responsible for the dysfunctional myelin found in schizophrenia spectrum disorders [359]. Interestingly, the authors found no lipid differences between controls and schizophrenic patients in cerebellar cortex, pointing to the possible regional specificity of Pl alteration in schizophrenia spectrum disorders.

4. Concluding remarks

As analyzed in this review, lipids are essential to brain function. Sterols, PUFA, sphingolipids, endocannabinoids and plasmalogens provide signaling cascades, second messenger synthesis, and the structural support to dendritic spines that are at the root of neural connectivity.

Adequate brain energy status during embryonic and postnatal development and infancy is essential, and its maintenance in adulthood is crucial for ensuring cerebral functions and cognitive performance through life.

Lipid metabolism alterations resulting from energetic failure contribute significantly to the synaptic dysfunction reported in many neurodegenerative disorders. Genomics and lipidomics have contributed to the identification of new diseases and syndromes associated with lipid synthesis and recycling disorders. We have discussed alterations in brain lipid homeostasis in AD, PD, Huntington disease, Niemann-Pick disease, and schizophrenia spectrum disorders. The list of diseases is however much longer: more than 80 disorders of complex lipid metabolism have been reported in humans. Additionally, we have briefly commented on membrane excitability defects and how the ECB system is finely regulated. New research into brain lipid homeostasis will contribute to emerging therapeutic strategies aimed at improving or preventing neurodevelopmental and age-related cognitive decline by promoting neurogenesis and counteracting the loss of synaptic connectivity and networking in aging and in neurodegenerative diseases.

Funding

No funding is associated with this review.

CRediT authorship contribution statement

F.J.B. and A.S.V. conceived the work, searched the literature, and wrote the manuscript.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

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