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Review

Brain membrane lipids in major depression and anxiety disorders ☆

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ABSTRACT

Major depression and anxiety disorders have high prevalence rates and are frequently comorbid. The neurobiological bases for these disorders are not fully understood, and available treatments are not always effective. Current models assume that dysfunctions in neuronal proteins and peptide activities are the primary causes of these disorders. Brain lipids determine the localization and function of proteins in the cell membrane and in doing so regulate synaptic throughput in neurons. Lipids may also leave the membrane as transmitters and relay signals from the membrane to intracellular compartments or to other cells. Here we review how membrane lipids, which play roles in the membrane's function as a barrier and a signaling medium for classical transmitter signaling, contribute to depression and anxiety disorders and how this role may provide targets for lipid-based treatment approaches. Preclinical findings have suggested a crucial role for the membrane-forming n-3 polyunsaturated fatty acids, glycerolipids, glycerophospholipids, and sphingolipids in the induction of depression- and anxiety-related behaviors. These polyunsaturated fatty acids also offer new treatment options such as targeted dietary supplementation or pharmacological interference with lipid-regulating enzymes. While clinical trials support this view, effective lipid-based therapies may need more individualized approaches. Altogether, accumulating evidence suggests a crucial role for membrane lipids in the pathogenesis of depression and anxiety disorders; these lipids could be exploited for improved prevention and treatment. This article is part of a Special Issue entitled Brain Lipids.

1. Introduction

With lifetime prevalences of more than 10%, major depressive disorder and anxiety disorders are common mental disorders [12]. These disorders lead to significant suffering for the affected persons and, therefore, belong to the leading diseases in the study of the total global burden of disease [221]. Approximately 10% of patients with depression commit suicide. The causes of these disorders are poorly understood. In this review, we summarize the current status of the relationship between lipids and depression and anxiety disorders.

Lipids play an increasingly recognized role in neuronal function in the brain [21]. The lipid composition of the brain (within single brain regions, specific neuronal subtypes, or even neuronal subcompartments) substantially influences subjective perception, mood and emotional behavior. A large number of lipids can be found in the plasma membrane,

Abbreviations: AC, acid ceramidase; ACTH, adrenocorticotropic hormone; AMPA, alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; ASM, acid sphingomyelinase; BDNF, brain-derived nerve growth factor; CB1, cannabinoid 1 receptor; CDP-DAG, cytidine diphosphate diacylglycerol; Cer, ceramide; CerS, ceramide synthases; COPI, coat protein complex I; DA, dopamine; DAG, diacylglycerol; DAT, dopamine transporter; DGK, diacyglycerol kinases; DHA, docosahexaenoic acid (22:6n-3); DOPAC, dihydroxyphenylacetic acid; DPA, docosapentanoic acid (22:5n-6); EPA, eicosapentanoic acid (20:5n-3); EPM, elevated plus maze; ERK, extracellular signal-regulated kinase; FA, fatty acids; FC, frontal cortex; 5-HT, serotonin; 5-HIAA, 5-hydroxyindoleacetic acid; FST, forced swim test; GalCer, galactosylceramide; GlcCer, glucosylceramide; GSL, glycosphingolipids; HVA, homo-vanillic acid; IFNα, interferon α; IL-6, interleukin-6; LPC, lysophosphatidylcholines; MAO, monoamine oxidase; Mfsd2a, major facilitator superfamily domain-containing protein 2; MHPG, 3-methoxy-4-hydroxyphenylglycol; NA, noradrenaline; Nac, nucleus accumbens; NAT, noradrenaline transporter; NMDA, N-methyl-D-aspartate; NSF, novelty suppressed feeding test; NSM, neutral sphingomyelinase; PA, phosphatidic acid; PC, phosphatidylcholines (*synonym*: glycerophosphocholines); PE, phosphatidylethanolamines (*synonym*: glycerophosphoethanolamines); PFC, prefrontal cortex; PI, phosphatidylinositols (*synonym*: glycerophosphoinositols); PIP, phosphoinositides (*synonym*: phosphatidylinositol phosphates); PI3K, PI-3-kinase; PKC, protein kinase C; PLA_2, phospholipase A2; PLC, phospholipase C; PLD, phospholipase D; PS, phosphatidylserines (*synonym*: glycerophosphoserines); PTEN, phosphatase and tensin homolog; PUFAs, polyunsaturated fatty acids; SERT, serotonin transporter; SM, sphingomyelin; SNPs, single nucleotide polymorphisms; S1P, sphingosine-1-phosphate; SPC, sphingosylphosphorylcholine; SphK2, sphingosine kinase 2; SSRI, selective serotonin reuptake inhibitor; TNF-α, tumor necrosis factor alpha; TPH-2, tryptophan hydroxylase-2

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where they regulate the membrane's function as a barrier between the intracellular and extracellular spaces. Membrane lipids can also determine the localization and function of proteins within the membrane and in doing so regulate synaptic throughput. Lipids can influence both exo- and endocytic processes and work within the membrane as second messengers. Lipids may be hydrolyzed and leave the membrane in both directions: as intracellular transmitters, they can relay signals from the membrane to intracellular compartments, and as extracellular transmitters, they can relay information to other cells. This review will focus on membrane lipids, which play roles in the membrane's function as a barrier and a signaling medium for classical transmitter signaling. An overview of the role of membrane-derived extracellular signaling lipids in synaptic function and emotional behavior can be found in other reviews [31,178,223]. The organization of this review follows the lipid classification of LIPID MAPS [56,57].

Membrane lipids have important functions in the brain. Membrane lipids constitute a physical barrier that segregates the inner and outer cellular environments; these lipids are also involved in cell signaling [210]. The lipid fraction of mammalian membranes consists of glycerophospholipids, sphingolipids and the sterol lipid cholesterol. The relative proportions of these components vary a great deal depending on the cell type and the type of membrane [71,210]. Glycerophospholipids use glycerol as a backbone, which carries two long-chain fatty acids (FA) attached at the *sn*-1 and *sn*-2 positions primarily through ester linkages (therefore called *diacylglycerophospholipids*). Polyunsaturated fatty acids (PUFAs) are preferentially attached to the *sn-2* position, while the FA at *sn-1* is usually saturated. The *sn*-3 position is occupied by one of several head groups. The typical glycerophospholipids found in mammalian membranes are phosphatidylcholines (PC; *synonym*: glycerophosphocholines), phosphatidylethanolamines (PE; *synonym*: glycerophosphoethanolamines), phosphatidylserines (PS; *synonym*: glycerophosphoserines) and phosphatidylinositols (PI; *synonym*: glycerophosphoinositols) that are all attached through a phosphodiester linkage. Depending on the cell type, a substantial portion of glycerophospholipids consists of plasmalogens (*1-alkyl,2-acyl glycerophospholipids*) that bear an ether-linked alkyl chain at the *sn*-1 position instead of the ester-linked FA [147]. Plasmalogens are especially abundant in the adult human central nervous system [147] and are thought to play a role in Alzheimer's disease [77]. Sphingolipids, the other abundant lipid category in plasma membranes, are synthesized from ceramide (Cer). Cer is composed of the long-chain amino alcohol sphingosine and a long saturated FA (C16–C32) attached to the 2-amino group via an amide linkage. The major sphingolipids in mammalian membranes are sphingomyelin (SM) and the glycosphingolipids (GSL), which contain mono-, di- or oligosaccharides based on glucosylceramide (GlcCer) or galactosylceramide (GalCer) [114]. Gangliosides are GSL with terminal sialic acids. They are expressed at high abundance and complexity in the brain [186,209]. Cerebrosides are either GlcCer or GalCer and play an important role in myelin function and stability [33].

The lipid classes contribute differentially to the bilayer assembly and the structural demands of biological membranes [210]. The lipid classes also differ in their ability to interact with proteins embedded in the membrane. Recently, a direct and highly specific interaction of exactly one SM species, *N*-stearoyl sphingomyelin (SM 18), with the transmembrane domain of protein p24, a protein involved in coat protein complex I (COPI) vesicle biogenesis, was demonstrated [36], indicating that membrane lipids can act as cofactors to regulate protein function. The acidic phospholipids PS and PI, which are preferentially located in the inner leaflet of the plasma membrane, are specifically recognized by soluble proteins [120]. The association of proteins with the surface of the intracellular membrane is essential for a wide variety of cellular functions. A small portion of the PI pool is further phosphorylated at the 3-, 4- and/or 5-positions to generate one of seven different phosphoinositides (*synonym*: phosphatidylinositol phosphates, PIPs). These lipids can be hydrolyzed into second messengers that mediate acute responses [15] or act as constitutive signals that define organelle identity [47].

The signaling-induced activation of hydrolytic enzymes can lead to the conversion of structural membrane components into regulatory messengers. PC can be converted into phosphatidic acid (PA) through the action of phospholipase D (PLD). PC-specific and PI-specific phospholipase C can remove the head group of phospholipids to yield diacylglycerol (DAG). SM can be converted to Cer by one of several sphingomyelinases. PA, DAG and Cer retain the full hydrophobic portion of their parent molecules and thus remain part of the membrane. They exert their regulatory function either through the recruitment of cytosolic proteins or by changing the biophysical properties of the membrane. In contrast, the removal of a FA from either glycerophospholipids or sphingolipids yields molecules that can readily leave the membrane. Examples include the production of a variety of lysophospholipids (*synonym*: monoacylglycerophospholipids) from their respective glycerophospholipids through the action of phospholipase A_2 (PLA_2), sphingosylphosphorylcholine (SPC) from SM via sphingomyelin deacylase [143] and sphingosine from Cer via ceramidase. Most of their regulatory function can be attributed to their binding to specific receptors. The FA released by these hydrolyses can further act in signal transduction, e.g., PUFA can be converted into eicosanoids.

2. Fatty acids

2.1. Preclinical evidence

The lipid composition of the brain can be altered with long-term changes in diet. This effect may have direct consequences on mood and emotional behavior. A highly palatable diet particularly rich in fat and low in proteins (often called the “cafeteria diet”) fed to rats for 8 weeks after weaning induced overweight status, higher adiposity, and a higher liver weight, as well as a reduction in anxiety-like behaviors in the open field and elevated plus maze (EPM) anxiety tests. This diet has also been shown to reduce general locomotor activity but increase social interactions and aggression, reduce pain threshold [22,116,168], and potentiate the anxiolytic effects of repeated foot shock stress [160]. These findings suggest that enhancing the general availability of lipids in the brain may have an anxiolytic/antidepressant effect. Nonetheless, the anxiolytic potential of this diet may be age-dependent and gender-specific with stronger effects in females [116,218]. The maternal intake of a high-energy diet enriched in PUFAs induced higher locomotor activity in the open field, increased levels of aggressive behavior in the resident intruder test, and had antidepressant-like effects in the forced swim test (FST) in mouse offspring [177].

The dietary effects on locomotor activity may thus depend on when PUFAs are enriched during development. Increased locomotion may occur if the supply is high during the prenatal time and weaning. The opposite effect can be observed if PUFAs are chronically increased only after weaning. Interestingly, a diet that was highly palatable due to an increased carbohydrate content also increased body weight and fat mass in rats but increased anxiety-like behavior in the light–dark test [197]. The anxiolytic/antidepressant effect of a diet is hypothesized to result not primarily from its palatability and increased expression of eating behavior but rather an increased lipid supply [168]; however, see also [137]. A study on susceptibility to chronic unpredictable stress, which may trigger depression-related behavior [164,222], suggested that the combination of a high-fat plus high-carbohydrate diet most effectively protects rats against a stress-induced increase in corticosterone levels [226].

Brain membranes contain a high proportion of PUFAs, with n-3 FA being the most prevalent in the brain's gray matter [20,193]. n-3 PUFAs cannot be synthetized de novo by mammals but must be obtained from the diet. The incorporation of these FA into the brain

occurs most efficiently during the suckling period and requires more time during adulthood [176,192,193]. When the brain levels of docosahexaenoic acid (DHA; 22:6n-3) in phospholipids are reduced by a diet, a compensatory increase in docosapentanoic acid (DPA; 22:5n-6) levels is usually observed [28,45,64]. The effects of n-3 FA deprivation on brain content and behavior can accumulate over the duration of a diet and over several generations [124,145]. Interestingly, a DHA depletion diet affects the brain's DHA content in a region-selective manner with the pituitary gland, cortex, hippocampus, cerebellum and striatum being the most severely affected brain areas [28,122,224]. Cortex, hippocampus, striatum and recently also the cerebellum are brain areas serving a multitude of different functions in behavioral organization and performance, and dysfunction of them was associated with depression [49,113].

2.1.1. The lack of n-3 polyunsaturated fatty acids in the brain induces depression/anxiety

Selective dietary deprivation of the n-3 FA DHA over several generations or post-weaning has consistently been shown to increase the expression of depression/anxiety-like behavior in the FST, novelty suppressed feeding test (NSF) and EPM test largely without affecting general locomotor activity in rats and mice [28,45,84,203]. However, there are also opposing findings [60]: a two-generational diet that was deficient in α-linolenic acid, the precursor of DHA, did not significantly affect locomotion or anxiety-related behavior in the EPM test in adult and old rats [13] or in mice [149,216]. The response to hedonic stimuli appears to be reduced in mice that received a two-generational diet deficient in n-3 FA. The deficient mice showed a lower sucrose preference in the sucrose preference test and a rightward shift in the dose–response curve for a morphine reward measured in a conditioned place preference paradigm. This finding was interpreted as a diet-induced anhedonic state [65]. Altogether, the majority of studies suggest that a lack of n-3 FA in the brain induces depression/anxiety-related behavior in animal studies.

Current hypotheses of the neurobiological mechanisms underlying anxiety and depression assume dysfunction in the brain's monoaminergic transmitter systems [130,181] in stress-mediating neuropeptides [185] or neurotropic factors [49] as well as a deregulation of hippocampal neurogenesis [131], which may act in concert or alone. Membrane lipids interfere with and possibly control all these processes and may provide a key mechanism for how membrane lipid composition can influence complex depression/anxiety-related behaviors.

2.1.2. Dopaminergic mechanisms

A reduction in brain DHA levels was paralleled by significant effects on monoaminergic neurotransmission in the frontal cortex (FC) but not in the (dorsal) striatum or cerebellum of rats. Dopamine (DA) tissue levels and the specific binding of DA to D_2-, but not D_1-receptors were significantly reduced in the FC. This effect may suggest a deficit in cognitive function and emotional evaluation of external stimuli. The activity of the monoamine transmitter metabolizing enzymes (monoamine oxidase (MAO) A and B) were not altered in the FC, striatum, or cerebellum of rats [43,44,230]. The effects of a dietary reduction in brain DHA levels were confirmed in piglets that were fed a diet deficient in linoleic and linolenic acid from birth to day 18. DHA-deficient animals showed lower FC tissue levels of DA and of the DA metabolites dihydroxyphenylacetic acid (DOPAC) and homo-vanillic acid (HVA) [42]. McNamara et al. [141] reported an increased DA turnover (DOPAC/DA ratio) in the prefrontal cortex (PFC) after perinatal DHA deficiency in rats. A morphological analysis revealed that DHA deficiency did not change the synaptic density or clear vesicle density in the FC of rats. However, DHA deficiency reduced the number of DA-filled vesicles at presynaptic terminals [229]. Other authors reported a reduction in tissue DA levels only within the first week after birth in the cerebral cortex, hippocampus, and striatum in two-generation DHA-deficient rats. No effect on DA in the FC, hypothalamus, hippocampus, temporal lobe, brain stem, or ventral striatum was found in rats after perinatal DHA deficiency [123,141]. In-vivo microdialysis studies revealed that a DHA deficiency attenuated extracellular DA levels at baseline conditions in the FC, but increased it in the Ncl. accumbens (Nac)/shell. The extracellular levels of DOPAC and HVA were increased in the FC and reduced in the Nac. While the DHA deficiency did not affect KCl-stimulated DA release or DA transporter (DAT) binding and function, it significantly reduced the amphetamine-induced DA response in the FC and Nac [107,230]. This effect may suggest that the maximal response capacity in core regions for the processing of the emotional and rewarding value of external stimuli and cognition is reduced. The expression of vesicular monoamine transporter 2 mRNA was significantly reduced in both brain regions, which suggests a reduced filling of vesicles with transmitters. When the vesicular stores were depleted with reserpine and the extracellular DA levels fell below the detection range, an amphetamine-induced DA increase was significantly increased in the Nac of the DHA-depleted animals (and less so in the FC). This effect may be due to the increase in the immunoreactivity of tyrosine 3-monooxygenase, which is one of the enzymes involved in DA synthesis in the ventral tegmental area (the origin of dopaminergic projections). Additionally, D_2- but not D_1-receptor-selective binding was increased in the Nac [228,231]. An imbalance of D_1 and D_2 signaling in the Nac may crucially affect processing of salient stimuli, and by that way contribute to depressive symptoms. While D_2-receptor mRNA expression was reduced in the FC, it was increased in the Nac of the DHA-depleted animals, suggesting distinct adaptations in the mesocortical vs. mesolimbic DA projections. Another study, however, found a reduction in D_2-receptor affinity and binding density in the ventral striatum (Nac plus olfactory tubercle) of female rats with a 20–22% brain DHA deficiency. D_1-receptor binding potential and affinity and D_3-receptor concentration did not differ in the ventral striatum. In the caudate putamen, a brain area controlling largely automatized behaviors, D_1-receptor binding and affinity showed an interaction with DHA deficiency and the reproductive status of female rats, while there was no change in D_2-receptor parameters. In this study, DHA deficiency was not observed to affect DA tissue levels [41]. The overexpression or knockdown of the D_2 receptor in the Nac did not significantly affect general locomotor activity or anxiety-related behavior in rats [61]. Overall, the majority of findings suggest that dopaminergic adaptations in the mesocortical DA system could play a major role in DHA deficiency-induced emotional dysregulation.

2.1.3. Serotonergic mechanisms

A reduction in brain DHA levels was paralleled by an increased binding specifically at the serotonin$_2$ (5-HT$_2$) receptor in the FC. However, 5-HT tissue levels and 5-HT-metabolizing enzyme levels were unchanged following DHA reduction [43,44,230]. The effects of the dietary reduction of brain DHA levels were investigated in piglets that were fed a diet that was deficient in linoleic and linolenic acid from birth to day 18. DHA-deficient animals showed lower tissue levels of 5-HT and its metabolite 5-hydroxyindoleacetic acid (5-HIAA; [42]). The effects on tissue 5-HT activity appeared to depend on the timing of the DHA deficiency. McNamara et al. [140] reported that a perinatal deficiency resulted in a decrease in 5-HT tissue levels and an increase in 5-HT turnover in the PFC of rats, while a post-weaning deficiency caused an increase in 5-HT tissue levels [140,141]. No effect was found when the DHA deficiency was induced at a post-pubescent age. Neither a perinatal nor post-weaning DHA deficiency changed 5-HT transporter (SERT) or 5-HT$_{1A}$-receptor mRNA expression in the mesencephalon. However, a perinatal deficiency was paralleled by a regional decrease in tryptophan hydroxylase-2 (TPH-2) expression [140]. The effect of a brain DHA reduction on 5-HT tissue levels appears to depend on the female's reproductive status. Levant and colleges [123] reported a decrease in 5-HT tissue levels in the FC in virgin rats but an increase in parous female rats after DHA deficiency. No changes were found (independent of the reproductive status) regarding 5-HT levels in the

hypothalamus, hippocampus, temporal lobe or brain stem. While 5-HT_{1A}-receptor binding density (B_{max}) in the hippocampus was slightly reduced in virgin rats, it was significantly increased in the parous female rats. No effects were found on 5-HT_{1A}- or 5-HT_{2A}-receptor binding or affinity (K_D) in the FC. The DHA deficiency partially increased depression-like behavior in the parous animals but had no significant effect in virgin rats [123]. A DHA deficiency had no effect on 5-HT_{1A}-, 5-HT_{2A}-, or 5-HT_{2C}-receptor mRNA expression in the PFC or on mesencephalic 5-HT_{1A}-receptor, SERT or TPH-2 mRNA expression in rats [1]. Altogether, there appeared complex effects of DHA deficiency on the serotonergic activity, which may essentially depend on when during development the deficiency occurred. For full understanding of DHA effects on 5-HT synaptic function, however, more research is still required.

2.1.4. Noradrenergic mechanisms

A reduction in brain DHA levels was paralleled by preserved noradrenaline (NA) tissue levels in the FC of rats [43,44,230]. No effect on NA turnover (3-methoxy-4-hydroxyphenylglycol (MHPG)/NA ratio) in the ventral striatum or hypothalamus was found in rats after perinatal DHA deficiency [141]. NA tissue levels, in contrast, were reduced from the second week after birth in the cerebral cortex, hippocampus, and striatum in DHA-deficient animals [202]. A DHA deficiency was shown to reduce midbrain NA transporter (NAT) mRNA expression and to increase α_{2A}-adrenoceptor mRNA expression [1]. Treating astrocytes from primary rat cerebral cultures with DHA increased the number of β-adrenoceptors [100].

2.1.5. Other mechanisms

DHA deficiency has wide-ranging consequences for protein expression in the brain. In the hippocampus, 114 proteins (out of 1008 measured) were differentially expressed in DHA-deficient animals. The cellular processes most affected by these proteins were neuritogenesis, endocytosis, and exocytosis. However, these proteins were also involved in mitochondrial dysfunction and clathrin-mediated endocytosis [55]. A decrease in brain DHA content was associated with a reduction in hippocampal brain-derived nerve growth factor (BDNF) mRNA expression and with BDNF protein levels in female rats [123]. A diet-induced deficiency in brain DHA levels may also act via indirect pathways for depression/anxiety-related behavior. A perinatal DHA deficiency was associated with significantly higher plasma interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF-α) levels in rats, both of which could be rescued through normalization of the DHA status as adults [141]. Other mechanisms through which PUFAs control neuronal function include the modulation of enzymes [146], voltage-gated ion channels [19], and endocytosis [167].

Despite the enrichment of DHA in brain phospholipids, it cannot be synthetized de novo in the brain but has to be transported from the blood into the brain. Recently, the major facilitator superfamily domain-containing protein 2 (Mfsd2a) was identified as a sodium-dependent transporter of DHA into the brain. Mfsd2a is localized exclusively in the endothelium of the microvessels of the blood–brain barrier [150]. Mice deficient in Mfsd2a (Mfsd2a knockout (KO)) showed a reduced brain volume. In particular, the hippocampal volume and number of neurons in the CA1 and CA3 regions were significantly reduced. Mfsd2a KO mice contained a significantly lower percentage of DHA but increased levels of arachidonic acid in brain phospholipids. These mice displayed a massive increase in anxiety-related behavior in the zero-maze, the light–dark test and in the open field. However, general locomotion, which always interacts with anxiety measures in these tests, was significantly reduced as well. Interestingly, these deficits could not be rescued by a DHA-rich diet to the mothers during development [150]. These findings suggest that a reduced uptake of DHA into the brain and subsequent DHA deficit during development results in macro- and micro-morphological deficits in the brain and increased anxiety in adulthood.

2.1.6. Increased n-3 polyunsaturated fatty acids reduce depression/anxiety

Several studies have reported on the antidepressant effects of n-3 FA in normal, i.e., non-depressed animals [121]. An n-3 FA-rich diet for more than 28–30 days, but not after shorter or acute treatments, reduced depression-like behavior in rats in the FST [27,92,115] and the light–dark test of anxiety [29]. This was paralleled by an increase in α-linolenic acid and DHA levels in the brain. Notably, brain DHA levels were negatively correlated with depression-like behavior (immobility) in the FST test [92]. For adult rats, supplementation with a diet rich in n-3 FA had antidepressant effects in the FST regardless of whether the supplements were provided during pregnancy and lactation (to the mothers) or during post-weaning and adulthood [63]. Maternal supplementation with an n-3 FA-rich diet reduced depression-like behavior in male offspring rats post weaning and at adult ages in the FST without affecting general locomotor activity in the open field test [215,217]. This effect was 5-HT- and 5-HT_{1A}-receptor dependent; pre-treatment with the 5-HT-synthesis inhibitor para-chlorophenylalanine or with the 5-HT_{1A}-receptor antagonist WAY 100135 blocked the effects of the diet. The n-3 FA-rich diet increased hippocampal and cortical BDNF concentrations at both ages in the offspring. The effects on tissue 5-HT activity, however, appeared to be age-dependent. Post-weaning, hippocampal 5-HT and 5-HIAA levels were reduced in the supplemented animals. At an age of 90 days, 5-HT levels were increased, but 5-HIAA levels remained attenuated [215]. A diet enriched in n-3 FA for 12 weeks was shown to reverse the decline in hippocampal neurogenesis in old rats [51]. A two-generational diet enriched with n-3 PUFAs significantly increased DHA levels in the striatum and hippocampus but not in the FC or cerebellum of rats. While NA levels were preserved in all four regions, 5-HT and DA tissue levels were increased in the FC. Animals with increased brain DHA levels showed significantly reduced spontaneous locomotion but no change in anxiety-related behavior in the EPM [30]. A study by Venna et al. [214] showed that supplementary treatment with n-3 FA for more than 5 weeks had antidepressant effects in the FST, tail suspension test, and NSF test in male mice. Interestingly, the effects were observed without any significant increase in FA in the brain. However, this chronic n-3 FA supplementation increased (1) hippocampal volume, (2) synaptophysin and BDNF expression in the CA1 and CA3 regions of the hippocampus and (3) the number of newborn cells in the dentate gyrus [214]. An in vitro study showed that DHA but not DPA increased neurite length and branch number in primary hippocampal neurons in rats [25]. A recent study reported that a 6-week diet with a high n-3/n-6 PUFA ratio reduced contextual fear memory in mice. The diet had no effect on the extinction of this memory. Brain and serum n-3/n-6 PUFA levels correlated negatively with contextual fear memory. Interestingly, this diet had no effect on body weight, locomotor activity or trait anxiety levels. The protective effects of the high n-3/n-6 ratio diet were mediated by an increased sensitivity of cannabinoid 1 (CB1) receptors in the basolateral amygdala, which increased short-term synaptic plasticity in this region [215].

Altogether, these findings suggest an important role of the hippocampus, its serotonergic innervation in particular, and of BDNF activity and neurogenesis for how n-3 FA reduces depression/anxiety-related behaviors. For conditioned anxiety, the basolateral amygdala and CB1 activity emerged as important mechanisms of n-3 FA action. However, it should be noted that the mechanisms explaining how increased DHA levels in the membrane affect these processes have only started to emerge and require more mechanistic research [38].

2.1.7. n-3 polyunsaturated fatty acids in the depressed/anxious organism

Depression and anxiety can be induced by environmental factors such as traumatic events or chronic stress [118,188]. These factors have been shown to disrupt the regulation of lipid synthesis [32]. Several animal models of depression have tested the effects of a

reduced or increased nutritional lipid supply on depression-related behaviors [105].

Isolation stress, induced by separately housing animals, induces depression-like behavior in the NSF test in mice. A two-generational diet deficient in n-3 PUFAs did not affect general locomotor activity and did not worsen the stress-induced depression-like behavior [84]. In contrast, the anxiety induced by early maternal separation stress was increased in adult rats after receiving an n-3 FA-deficient diet [139]. Sucrose preference, a measure of the hedonic response of animals, was synergistically increased via maternal deprivation stress and brain DHA depletion [139]. These findings suggest that a deficiency in DHA levels in the brain may have no effects or negative effects in a depressed/anxious organism.

Chronic mild stress over several weeks can induce depression-like behavior in rodents [164,222]. Chronic mild stress for 8 weeks led to the deterioration of the coat state and a reduction in the body weight of mice. While chronic mild stress did not significantly affect depression-like behavior in the NSF test, it reduced the latency of agonistic behavior in the resident intruder test. Chronic mild stress did not affect DHA levels in the brain but did reduce the brain content of DPA in the FC, hippocampus, and striatum. It also significantly reduced tissue levels of NA in the FC and striatum [211]. A dietary supplementation with n-3 PUFAs significantly increased DHA levels in the FC and hippocampus and reduced DPA levels without having major effects on behavior. In the stressed animals, n-3 PUFA supplementation increased tissue 5-HT levels in the FC and hippocampus but not in the striatum [211]. This study suggests that the protective effect of n-3 PUFAs could act by enhancing 5-HT activity in the FC and hippocampus.

Restraint stress is another model to induce depression-like behavior in rodents, as measured in the FST and EPM tests in a study in male rats. Dietary supplementation with n-3 PUFAs from day 21 to day 134 had significant antidepressant effects. This treatment reversed the behavioral effects of the restraint stress in both behavioral tests. There was also a normalization of the stress-induced increase in plasma corticosterone levels, which serves as a potential mechanism for the antidepressant effects [62].

In a rat model of postpartum depression, female rats showed an increase in immobility in the FST, an increase in hippocampal corticosterone levels and an increase in pro-inflammatory cytokines. These effects could be significantly reduced through a 15-day treatment with n-3 FA via menhaden fish oil. The effects of the n-3 FA at the highest treatment dose (9 g/kg/d) resembled that of a 15-mg/kg/d fluoxetine treatment [10]. Fish oil supplementation to mothers during mating, gestation and lactation reduced the anxiety-like behavior induced by olfactory bulbectomy in the male rat offspring [169].

The decline in food-motivated operant behavior and social exploration after the peripheral administration of a bacterial lipopolysaccharide was attenuated by the pre-feeding of an n-3 PUFA-rich diet in male mice [219]. The protective effect of an n-3 PUFA-rich diet was also found in another model of inflammation. The injection of zymosan induced acute peritonitis and behavioral depression. The attenuation of food-maintained operant response after zymosan treatment was reduced via pre-feeding with an n-3 PUFA-rich diet in male mice [201].

2.2. Clinical evidence

The human peripheral lipidome, with thousands of distinct lipid molecular species, is well characterized [174]. However, data are scarce on the composition of brain lipids because material is limited to post-mortem samples or tissue from patients undergoing brain surgery; there are also few modern neurospectroscopic options for the analysis of specific components (for example choline-containing lipids).

Adult neurogenesis (the continual generation of new functional neurons throughout postnatal life) is primarily localized in the dentate gyrus of the hippocampus and is essential for the brain's normal function. The disruption or ablation of this process can lead to severe impairments including depressive [53,142,196] and anxiety-related behavior [39,179]. The close contact of the underlying neural stem cells with local blood vessels is assumed to facilitate the delivery of biochemical stimuli, such as food-derived components from the systemic milieu, to this brain region. In this light, a vast number of studies support the hypothesis that the brain's structure and function may be modulated by specific aspects of the diet, including frequency, content and total energy intake throughout the organism's lifespan. Therefore, dietary interventions have emerged as effective environmental inducers of neuronal plasticity, and a vast body of literature has focused on the effect of n-3 long-chain PUFA supplementation on cognitive and emotional regulation; this literature has obtained incongruent results.

The intake of n-3 long-chain PUFAs found in oily fish (as the principal source) in modern Western diets is suboptimal; however, the consumption of oils and foods rich in n-6 long-chain PUFAs has increased [191]. The resulting lower ratio of n-3 to n-6 long-chain PUFAs has been implicated in the etiology of psychiatric disorders such as depression [87]. A number of parallels have been observed between the neural systems affected by an n-3 PUFA deficiency and those altered in depression; these systems include neurotransmission, glucose and amino acid metabolism, the levels of BDNF and proinflammatory cytokines as well as neuronal atrophy [194]. The likelihood of depressive symptoms as estimated via the Beck Depression Inventory with an adjustment for potential confounders was significantly higher among 3204 Finnish adults who were infrequent fish consumers [204]. A lower fish intake was also associated with a higher risk of suicide in a study of Japanese men [88]. A robust correlational relationship between greater seafood consumption and lower lifetime prevalence rates of bipolar I and II disorders and bipolar spectrum disorder was found in a cross-national context [151]. Early studies have already suggested an association between the blood measures of FA status and the severity of depression [3] as well as a depletion of n-3 FA levels, particularly DHA, in red blood cell membranes [165] and lowered n-3 PUFAs in the serum phospholipids and cholesteryl esters of depressed patients [129]. In elderly, community-dwelling individuals, FA composition was linked to depression when possible confounders such as inflammation or atherosclerosis were taken into account [205]. Both n-3 and n-6 PUFA levels were inversely correlated with impulsivity and depression scores in patients presenting with self-harm [72]. Somatically healthy patients suffering from major depressive disorder presented not only with a higher prevalence of conventional risk factors for cardiovascular diseases but also with significantly lower individual n-3 PUFAs and an overall reduced Omega-3 Index that was associated with high concentrations of IL-6 proinflammatory cytokine levels [11]. In patients recovering from acute coronary syndromes, those with major depression two months after discharge had significantly lower levels of total n-3 PUFAs and of DHA as well as higher ratios of arachidonic acid to DHA, arachidonic acid to eicosapentanoic acid (EPA, 20:5n-3) and n-6:n-3 ratio [67].

While changes in plasma/serum and red blood cell membranes mirror the FA consumed over short time periods [104], other studies have attempted to identify biomarkers for the habitual, long-term dietary intake of FA (in the range of a few years) as reflected in adipose tissue. In a preventive medicine and nutrition program, mildly depressed subjects had significantly reduced adipose tissue DHA levels compared with non-depressed participants. These findings suggest an association between an increased long-term dietary DHA intake and decreased depression as well as an inhibitory effect of DHA on the production of cytokines that are associated with depression [136]. In line with previous studies on adult and elderly subjects, adipose tissue 20:5n-3 EPA levels were also inversely correlated with depression scores in adolescents, indicating that a low long-term dietary intake of EPA is associated with an increased risk of depression [134]. However, other studies in healthy adults either failed to confirm these observations [135] or reported contradictory

results such as elevated levels of EPA and DHA in patients with endogenous depression [54].

A small non-significant benefit was found in a meta-analysis of 13 randomized placebo-controlled trials of n-3 FA treatment involving various doses of EPA and DHA in patients with a major depressive disorder. Most of the observed treatment efficacy was attributed to a publication bias and an association with trials of lower methodological quality, shorter duration, more severely affected participants and completers rather than intention-to-treat analysis [18]. However, the inclusion and exclusion criteria for study selection applied in this meta-analysis have been criticized [125,138] as other recent meta-analyses have found contradictory results [9,68,69,126,200].

A conclusive decision remains difficult due to the considerable heterogeneity of the trials. Available evidence indicates that subjects diagnosed with depression may benefit most from n-3 PUFA administration, whereas there is no sufficient indication of any benefit for individuals without a diagnosis of a depressive illness. In patients with unipolar depression, an 8-week treatment with EPA had therapeutic effects equal to those of fluoxetine. Furthermore, the combination of both EPA and fluoxetine was superior to either alone in reducing depressive symptoms [99].

In female bipolar disorder outpatients with moderate depressive symptoms receiving daily treatment with ethyl-EPA (the semi-synthetic derivative of EPA) for 12 weeks, quantitative proton magnetic resonance spectroscopy revealed significantly increased levels of cerebral N-acetylaspartate, a putative marker of neuronal integrity, in a specific region above the corpus callosum [66]. This report underlines a potential neurotropic role for ethyl-EPA in depression and calls for a more detailed investigation of its therapeutic potential and mechanism of action. The most recent comprehensive meta-analysis of randomized clinical trials using n-3 PUFAs to treat depressive disorders found that n-3 PUFA use was significant as an adjuvant rather than mono-therapy; this effect was independent of baseline depression severity, trial duration and patient age. However, there is insufficient evidence regarding the efficacy of n-3 PUFA in treating depressive symptoms in young or healthy subjects as well as in perinatal depression scenarios [78].

Due to their co-morbidity with depression, anxiety, stress and anger were often included as secondary outcomes in studies examining the effects of an n-3 PUFA diet on depression. The presence and severity of comorbid anxiety in medication-free patients diagnosed with major depressive disorder were associated with lower EPA and DHA levels and a higher ratio of arachidonic acid to EPA [127]. The potential of n-3 PUFA supplementation to preferentially alleviate major depressive disorders with more severe anxiety should be investigated in future studies.

In healthy adults, the Spielberger State-Trait Anxiety Inventory score was positively associated with the (linoleic acid + alpha-linolenic acid)/(arachidonic acid + EPA) ratio in adipose tissue. This correlation was thought to originate from the inhibitory role of catecholamines on delta 6 and delta 5 desaturases [133]. A randomized placebo-controlled trial in healthy young medical students demonstrated a reduction in anxiety symptoms and inflammatory markers after 12 weeks of supplementation with EPA and DHA [106]. In a different setting, the effect of n-3 PUFA administration on anxiety levels was assessed in substance abusers known for their poor dietary habits and because of the strong association between anxiety, aggression and substance use disorders. Compared with patients receiving placebo capsules, patients taking 3 g of DHA + EPA daily for three months showed a significant progressive decline in anxiety scores that remained decreased even three months after treatment discontinuation [23]. In a subsequent study, an n-3 PUFA treatment significantly decreased scores for anxiety and anger. Interestingly, an increase in the plasma levels of EPA was more strongly correlated with low end-of-trial anxiety scores, whereas the increase in plasma DHA was more strongly correlated with low end-of-trial anger scores [24].

A possible confounding factor in these studies is a genetic influence that has been suggested for the differential response of neurological disorders to treatment with ethyl-EPA [173]. In Huntington's disease, patients with a lower CAG repeat number in the Huntingtin gene showed greater clinical improvement with ethyl-EPA compared with the placebo group [172]. These pharmacogenetic effects of nutrients on individuals, labeled as “nutrigenomics”, could also hold true for patients suffering from psychiatric disorders. Although n-3 FA are classified as essential, their final bioavailability not only depends on dietary intake but also on the activity of metabolic pathways including enzymes that convert shorter- to longer-chain PUFAs. Polymorphisms in genes coding for FA desaturases 1–3, for example, result in either lower levels of n-3 or higher levels of n-6 long-chain PUFAs and have been associated with dyslipidemia and other cardiovascular risk factors [40].

In summary, a large number of observational and interventional studies indicate beneficial effects for n-3 long-chain PUFAs in the treatment of depression and anxiety. However, more research is required to determine the most potent type, dose, and duration of n-3 PUFA supplementation; additionally, the most potent treatment effects may be limited to specific patient subgroups. It should also be noted that from current mechanistic research it is not clear whether PUFA effects in depression and anxiety are mediated by changing membrane properties or by altered levels of PUFA-derived lipid signaling molecules [31,178,223].

3. Glycerolipids

3.1. Preclinical evidence

DAG is an important membrane signaling lipid in the brain. DAG is primarily generated through the hydrolysis of phosphatidylinositol-4,5-bisphosphate by phospholipase C (PLC). Once generated, DAG can activate numerous intracellular proteins such as protein kinase C (PKC), Ras guanyl nucleotide-releasing protein and the transient receptor potential cation channel. DAG signaling is terminated by diacyglycerol kinases (DGKs), which convert DAG to the lipid second messenger, phosphatidic acid (PA). DGKs modulate intracellular lipid signaling by terminating DAG's effects and by producing PA [206].

DGKβ is a member of the DGK family and is widely distributed in the brain. A high density of DGKβ was found in the neurons of brain areas associated with emotion such as the olfactory bulb, Nac, amygdala and hippocampus [26,75]. In the hippocampus, DGKβ was found in the postsynaptic regions of projection neurons as well as in GABAergic interneurons [90]. Membrane-bound DGKβ controls the lipid activity that regulates long-term potentiation, dendrite outgrowth and spine maturation in hippocampal CA1 neurons [90,190]. The elimination of DGKβ activity in a KO mouse model resulted in attention deficit and memory impairment [93,190]. However, these mice also showed psychomotor deficits. During the active period of the day, DGKβ KO mice showed significantly increased locomotor activity in their home cages. When tested in the open field, general activity was increased; however, the time spent in the center also increased, suggesting reduced levels of anxiety. These effects were confirmed in the EPM test in which DGKβ KO mice also showed reduced levels of anxiety and increased locomotor activity. Interestingly, sensorimotor gating (as measured via prepulse inhibition) and social interaction were not disturbed in DGKβ KO mice. The reduced anxiety and hyperactivity observed could be reduced using the mood stabilizer lithium in DGKβ KO mice [101]. These findings suggest a role for the intracellular lipids DAG and PA in the control of anxiety-related behaviors [89].

4. Glycerophospholipids

4.1. Preclinical evidence

Chronic unpredictable stress, which induces depression-like behavior in the FST and oxidative stress in the brains of mice, was shown to alter

the brain's phospholipid content. Stress significantly reduced the levels of PI but increased the levels of PC. The increase in PE was not significant [59]. These effects were observed throughout the entire brain. A more recent study suggests a brain area-specific regulation of phospholipid levels. Chronic unpredictable stress for 4 weeks led to a significant increase in hippocampal PI levels and a decrease in PE levels in the PFC of rats. No effects on phospholipid levels were observed in the amygdala or cerebellum [157]. These findings suggest that brain areas need to be considered separately in functional analyses.

Antidepressant drug treatment does not only affect monoaminergic systems but may also have profound effects on the phospholipid levels in the brain. PIPs, also called phosphoinositides, are involved in various downstream signaling pathways including DAG-regulated PKC activation, PI-3-kinase (PI3K)/Akt signaling, and inositol triphosphate-mediated calcium signaling. Cytidine diphosphate diacylglycerol (CDP-DAG) is an intermediate in the synthesis of PI. Imipramine, paroxetine, and maprotiline increased the levels of CDP-DAG and PI in neuron-like PC12 cells [2]. Several classes of antidepressant drugs dose-dependently increased CDP-DAG levels in the hippocampus, PFC, and striatum of rat brain slices; these classes include classical antidepressants (imipramine and desipramine), selective 5-HT reuptake inhibitors (SSRIs) (fluoxetine and paroxetine), and atypical agents (maprotiline and nomifensine). Other psychotropic compounds, such as the antipsychotic agents sulpiride, chlorpromazine, and haloperidol, or the anxiolytic agents diazepam and phenobarbital had no effect on CDP-DAG levels. The increased CDP-DAG levels were found to translate to an increased synthesis of PI and an accumulation of inositol phosphates in these brain regions [161,163,207,208]. To test whether this effect has any relevance in the antidepressant action of the investigated compounds, animals were pre-treated with neomycin (a PIP-inactivating polyhydroxylated aminoglycoside) and tested in the modified FST. Neomycin reduced the accumulation of newly synthesized PIP as well as the formation of inositol phosphates and blocked the antidepressant effects of imipramine, fluoxetine, and maprotiline [207]. Fluoxetine, imipramine and maprotiline also increased CDP-DAG levels in the FC and hippocampus of mice. This effect was at least partially 5-HT-dependent for fluoxetine but not for imipramine [2]. Overall, these studies suggest an important role for PIP in the action of antidepressant drugs.

PC are the most abundant phospholipids in membrane bilayers. Lysophosphatidylcholines (LPC) also have important roles in membrane permeability and fluidity. A lipidomic study in mice suggested that a daily intraperitoneal treatment with the antidepressant drugs maprotiline and paroxetine decreased PC species and increased LPC species in the PFC, which suggests an increase in PLA_2 activity. Interestingly, these effects were region-specific and were not observed in the hippocampus, striatum or cerebellum. These effects were suggested to lead to the release of DHA [119], which has independently demonstrated antidepressant effects (see above).

4.2. Clinical evidence

The reaction to mental and emotional stress is thought to play an important role in the pathophysiology of depression and anxiety. Healthy subjects were treated with different amounts of a complex of phospholipids containing PS, PC, PI, PE, lyso-phospholipids and PA. Treatment with a moderate dose significantly affected the pituitary adrenal reactivity (ACTH, cortisol) and the psychological response in a standardized stress test [86]. Glycerophospholipids therefore could be promising molecules for the treatment of stress-related disorders.

Several important second messengers can be derived from phosphorylated PI. Akt, a downstream kinase of PI, has been shown to be involved in depression and suicide [103]. To investigate the potential involvement of molecules upstream of Akt, alterations in PI3K activity were investigated in suicide victims. The role of PI3K in suicide was investigated post-mortem in the PFC, hippocampus and cerebellum at the messenger and protein levels. The catalytic activity of PI3K was significantly decreased in the PFC and hippocampus of psychiatric suicide victims compared with non-psychiatric non-suicide subjects. Of note, the reduced PI3K activation was similar for suicide victims of all psychiatric backgrounds, not only those with major depression. Thus, aberrant PI3K signaling appeared to be more indicative of suicide [50]. In a similar study, the enzymatic activities of PI3K and its antagonist PTEN were studied post-mortem in the PFC of suicide victims and non-suicide subjects. Here, irrespective of the suicidal background, depressed patients had a significant decrease in their PI3K and Akt activities compared with non-depressed non-suicide subjects [102]. Therefore, how the impaired phosphorylation of lipid second messengers contributes to the pathophysiology of depression and suicide remains to be established.

Serotonin and its receptors are highly involved in major depression and suicidal behaviors. The downstream signaling of 5-HT_{1A} receptor activation was investigated in post-mortem brain samples from depressed suicide victims. The activities of PI3K, Akt and PTEN were analyzed in membrane fractions of the occipital cortex upon stimulating 5-HT_{1A} receptors with an agonist using a biochemical radio-enzymatic assay. The activities of PI3K and Akt were significantly decreased in the occipital cortex of suicide victims, whereas the PTEN levels in suicide victims were higher compared with non-psychiatric non-suicide subjects. Alterations in 5-HT_{1A} receptor activation appeared to affect different downstream targets that could be important for deregulated cell survival processes [91]. The responsiveness of the 5-HT_{2A} receptor can be directly measured in the blood platelets of patients via serotonin-activated PI hydrolysis [180]. Depressed patients who made at least one suicide attempt were investigated. High-lethality attempters had a significantly lower platelet 5-HT_{2A} receptor response compared with low-lethality attempters. Therefore, high-lethality attempters appear to have a higher number of 5-HT receptors accompanied by impaired signal transduction [132]. The 5-HT_{2A}-induced hydrolysis of PI was also investigated in subtypes of depression. Cultured fibroblasts of patients with major depression with or without melancholia and healthy controls were analyzed. 5-HT produced a concentration-dependent increase in PI hydrolysis with a significantly lower maximum signal in the fibroblasts of melancholic patients, whereas non-melancholic patients did not differ from controls [5].

In a systems biology approach, the PI signaling pathway was investigated in the context of anxiety- and depression-like phenotypes based on transcriptome data that also included ortholog model organisms. PI signaling was implicated in anxiety-like phenotypes [74].

PC and its metabolites can be investigated in humans through the analysis of blood plasma. The association between choline concentrations in the plasma and non-pathologic symptoms of anxiety and depression were investigated in the Hordaland Health Study. Choline concentrations were found to be negatively correlated with anxiety symptoms but not with symptoms of depression in a general population sample [16]. In a recent lipidomic study, the association between different glycerophospho- and sphingolipid species and symptoms of anxiety and depression was investigated in a healthy Dutch family-based sample. Plasma PC levels, specifically the absolute levels of PC 36:4 and its ratio to Cer 20:0, were inversely correlated with symptoms of anxiety [46]. Thus, decreased PC and choline levels could be associated with anxiety, at least in a non-pathologic context.

Choline is an essential compound of the phospholipids PC and SM. Recently evolved neurospectroscopic methods enable the non-invasive measurement of choline-containing precursors and the products of membrane phospholipid metabolism in vivo [170]. Using 31-phosphorus neurospectroscopy, a severe case of treatment-resistant depression in a 21-year-old male was monitored prior to and after oral treatment with ethyl-EPA (4 g/d). After nine months, the patient's depressive symptoms had disappeared. Regarding the levels of PC-related molecules, there was a significant increase in membrane phospholipid anabolic precursors,

namely phosphocholine, phosphoethanolamine and phosphoserine, and a decrease in metabolites of phospholipid catabolism, namely glycero-3-phosphocholine and glycero-3-phosphoethanolamine; this observation indicated a reduction in neuronal phospholipid turnover due to the treatment [171]. In a proton neurospectroscopy study, children and adolescents suffering from major depression were investigated for choline-containing molecules. Depressed children had significantly lower levels of phosphocholine and glycero-3-phosphocholine in the right anterior cingulate compared with the control group [158]. Elderly people were studied in the context of late-life major depression. 31-phosphorus neurospectroscopy revealed an increase in glycero-3-phosphocholine in the white matter compared with the gray matter in elderly depressed patients. Therefore, white matter appears to be an important substrate for increased neurodegenerative processes. The metabolite glycero-3-phosphoethanolamine was significantly increased in the white matter of depressed elderly patients compared with the control group. This finding indicates an elevated breakdown of cell membranes in patients with late-life depression [85].

A proton neurospectroscopy study was also conducted in adults with bipolar disorder. Compared with healthy controls, patients had significantly higher levels of the choline-containing compounds phosphocholine and glycero-3-phosphocholine in the hippocampus and the orbitofrontal cortex. This observation may indicate increased membrane breakdown and neuronal loss in certain brain regions relevant to the pathophysiology of bipolar disorder [189]. Lecithin containing more than 90% PC has also been tested as a treatment for mania occurring in bipolar disorder. In a double blind, placebo-controlled study, an oral treatment with lecithin (10 mg, three times per day) for several alternating 1-week trials had a clear therapeutic effect. During the lecithin application, patients had significantly lower symptoms of mania as rated using different psychiatric assessment scales [34].

In recent discussions, mitochondrial dysfunction is thought to play a critical role in the pathophysiology of psychiatric syndromes. In a proton neurospectroscopy study, the levels of glycero-3-phosphocholine were investigated in various brain regions. Anxiety symptoms in mitochondrial patients correlated positively with glycero-3-phosphocholine levels in the hippocampus, which was not observed in the control group. This result could be indicative of an increased phospholipid breakdown and membrane degradation, which is promoted by mitochondrial dysfunction. Therefore, higher levels of glycero-3-phosphocholine could reflect hippocampal damage and the associated symptoms of anxiety [8].

The activity of PLA_2 was measured in the serum of psychiatric patients using a radio-enzymatic assay with PC as a precursor. Compared with the healthy controls, patients suffering from major depression and bipolar disorder displayed a significantly higher level of PLA_2 activity. However, because the level of PLA_2 activity also increases in patients with schizophrenia and substance abuse as well as with infections and inflammatory diseases, the increase in PLA_2 in depression should be interpreted with caution [152]. A recent study investigated the mRNA levels of PLA_2 in the peripheral blood cells of medicated patients with recurrent depressive disorder. The mRNA expression of PLA_2 type IIA was significantly increased compared with healthy controls. Because PLA_2 belongs to a pathway involved in inflammation, oxidative and nitrosative stress, these processes could be relevant in the pathophysiology of depression [70].

Several single nucleotide polymorphisms (SNPs) of the PLA_2 coding gene were investigated in the context of depression. Patients suffering from chronic hepatitis C viral infection under treatment with interferon α (IFNα) (which often leads to depressive symptoms) were analyzed, as were patients with major depression. The SNP rs10798059 was found to be associated with a higher risk of IFNα-induced depression and a higher level of somatic depression symptoms. The pathophysiology of depression could involve inflammatory mechanisms [199].

Bennet and Horrobin [14] presented an overview of the enzymes related to phospholipid metabolism that have a known chromosomal location and positive genetic findings linked to major psychiatric disorders in the same gene region. The gene coding for PLA_2 was found to be associated with risk genes for bipolar disorder in several studies, thus pointing to a potential role for PLA_2 in the pathophysiology of the disease. Additionally, the PLC signaling pathway was associated with bipolar disorder in both an initial and a replicated sample, as revealed in a recent meta-analysis of genome-wide association studies [156].

5. Sphingolipids

5.1. Preclinical evidence

Together with cholesterol and glycerophospholipids, sphingolipids are the most common lipids in brain membranes [94–96]. In addition to their role in forming a physical barrier, sphingolipids and cholesterol play an important role in receptor signaling. Together, they form lipid rafts, which are membrane compartments that are enriched in G-protein-coupled receptors. Lipid rafts can be considered to be lateral assemblies of sphingolipids and cholesterol in tight hydrophobic interactions with decreased levels of PC. Rafts are less fluid and gel-like compared with the liquid crystalline phospholipid bilayer [212,213]. Cholesterol, a privileged binding partner of sphingolipids, can through its alpha face interact with other lipids (e.g., SM) and through its beta face interact with transmembrane proteins such as neurotransmitter receptors. Changes in the composition of the lipid rafts may therefore directly affect receptor affinity, signaling and subsequent internalization [58,166,175]. Lipid rafts have been suggested to be specific sites for the activation of acid sphingomyelinase (ASM) and subsequent Cer generation in response to various stressors. Consequently, the hydrophobic Cer appears in patches on the cell surface; these patches rapidly merge to form larger platforms or macrodomains. These platforms bind membrane-related proteins, such as protein kinase C or c-Raf-1, and enable the oligomerization of specific cell surface proteins such as G-protein-coupled receptors [37,108].

Chronic unpredictable stress for 4 weeks increased Cer levels in the PFC and hippocampus of rats. SM levels were concomitantly decreased. As a result, serum corticosterone levels were inversely correlated with PFC SM levels. No significant effects were observed in the amygdala or cerebellum [157].

The role of sphingolipids in depression/anxiety was investigated in animal studies that used genetic approaches to manipulate the relevant anabolic and catabolic enzymes. Mice with a transgene for acid sphingomyelinase (tgASM) showed higher ASM activity and Cer production in the hippocampus [80]. The increased Cer levels in the hippocampus were paralleled by a decline in neurogenesis, neuronal maturation, and neuronal survival [80], which are depression-related neuronal markers [113,184]. There was also a reduction in Akt phosphorylation at Ser473 [80], which has been shown to control hippocampal neurogenesis [232]. A T308DS473Akt1 mutation in PC12 cells prevented the inhibitory action of C16 Cer on cell proliferation [80]. At the behavioral level, tgASM mice showed a depression/anxiety-like phenotype as measured using the coat status, NSF test, splash test, open field, light–dark box, and FST [80]; for a review, see [111].

Mice deficient in ASM (ASM KO) typically develop Niemann–Pick disease, a lysosomal storage disorder, in late adulthood. When tested prior to displaying signs of the disorder, homozygous ASM KO mice already presented reduced Cer levels in the hippocampus and showed signs of reduced anxiety and less severe depression-related behaviors. Genetically induced Cer hypo- or hyperfunction had no gross effects on synaptic structure. This change also did not impair synaptic function in the hippocampus [80]. Antidepressant drugs, many of which appear to be functional inhibitors of ASM [6,110,112], can normalize the effects of chronic unpredictable stress in wild type and tgASM animals but not in ASM KO mice.

The pharmacological inhibition of ASM with tricyclodecan-9-yl-xanthogenate inhibited IFNα-induced 5-HT uptake in T-cells [198]. This observation suggests that ASM (and its inhibition in particular) could be a major pathway for the pharmacological effects of antidepressants [80,111].

The pharmacological inhibition of neutral sphingomyelinase 2 (NSM2) with GW4869 reduced the level of multiple Cer species in the brain. NSM2 inhibition had no effect on episodic-like memory but did impair spatial reference memory in mice [220]. This effect was paralleled by changes in N-methyl-D-aspartate (NMDA) and alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor subunit composition as well as the membrane insertion of these receptors [220]. Conversely, neutral sphingomyelinase (NSM) application increased Cer levels, increased action potential frequency, and reduced the slow after-hyperpolarization in hippocampal slice preparations [153]. These effects are correlated with increased information processing in the hippocampus. An in vitro study showed that the pharmacological inhibition of NSM with sphingolactone-24 in T-cells inhibited IFNα induced 5-HT uptake [198]. This suggests an antidepressant effect of NSM inhibition.

Acid ceramidase (AC) metabolizes Cer in the brain. The pharmacological inhibition of ceramidase with LCL385 had no effect on depression-like behavior in the FST in rats [148]. In AC heterozygous KO mice, however, neurogenesis, neuronal maturation, and neuronal survival were significantly reduced and were paralleled by an increase in depression-like behavior [80].

While Cer is hydrolyzed by ceramidases, the sphingosine generated as a result can be re-acylated by ceramide synthases (CerS). In mammals, six CerSs have been described. In flincher mice, a spontaneous deficiency in CerS1 activity was identified. This alteration resulted in reduced total brain Cer levels and reduced C18 but increased C16 Cer levels. At the behavioral level, the CerS1 deficiency was associated with cerebellar and motor dysfunctions [227]. A genetically induced deficiency in CerS1 reduced C18 Cer levels in the cerebellum but increased C16 and C22 Cer levels, while the total Cer level was unaltered. These effects were associated with attenuated locomotor activity and reduced anxiety in the open field test. Impaired motor learning and spatial working memory were also reported [73]. A genetically induced deficiency in CerS6 in mice was associated with reduced C16 Cer levels in the thymus, small intestine, and kidney. However, there was only a small C18 Cer decrease observed in the cerebellum and no effect in the forebrain. CerS6 KO mice were hyperactive in a novel environment but did not display altered levels of anxiety-related behavior or changes in novel object recognition learning [52]. These findings suggest an involvement of Cer not only in anxiety-related behavior but also in locomotor activity and cognitive impairments. Taken together, the genetic and pharmacological evidence from preclinical studies suggests that Cer, which is constitutively controlled by ASM, NSM, AC and CerS activities, may critically control depression-associated neuronal mechanisms and behaviors.

SM and Cer are critical for the formation of lipid rafts and signaling platforms, respectively [79,108], which mediate monoamine receptor membrane localization, signaling and internalization [17,154,155,195]. While genetic approaches have addressed the role of Cer indirectly (i.e., by modulating its formation and metabolism), pharmacological approaches have provided a more direct approach. Repeated local injections of C16 Cer into the dorsal hippocampus of mice induced depression-like behavior in the NSF and sucrose preference tests [80]. This result is in line with the effects of chronic unpredictable stress, which not only doubled hippocampal Cer levels and reduced neurogenesis and neuronal maturation but also induced depression-like behavior in mice [80]. Cer application to rat hippocampal slices depressed long-term synaptic responses. This effect was mediated by ionotropic glutamate receptors [225].

While the available evidence points to a depression/anxiety-inducing effect of Cer abundance in the hippocampus, the antidepressant action of a pharmaco-treatment may not always function by reducing the hippocampal Cer content. A lipidomic study suggested that a daily i.p. treatment with the antidepressant drugs fluoxetine, maprotiline and paroxetine, which are functional inhibitors of ASM in the brain [110], had no significant effects on the hippocampal levels of Cer or SM. In the PFC, however, maprotiline and paroxetine reduced SM species and increased Cer species [119]. However, this study was conducted in normal mice, which do not show elevated levels of hippocampal Cer. The action of antidepressant drugs may therefore differ in a depressed/anxious organism.

GalCer is a major component of the myelin sheath in the brain. Early life stress, which is administered during early weaning, induces a significant but temporally restricted increase in GalCer at 5 weeks of age in mice. This effect was specific for the amygdala and not observed in the hippocampus or PFC. The changes in GalCer were associated with increased anxiety-like behavior in the EPM test at 5 and 8 weeks of age. These findings suggest that GalCer in the amygdala plays an important role in the development of a hyperanxious phenotype [159].

Cer can be hydrolyzed by one of several ceramidases to sphingosine, which can be phosphorylated to sphingosine-1-phosphate (S1P) by one of two sphingosine kinases [111,114]. Restraint stress in rats, which caused an increase in anxious behavior, increased the serum levels of S1P and sphinganine-1-phosphate but had no effect on sphingosine or sphinganine levels [97,98]. S1P is a powerful inducer of neurogenesis in the brain [7]. Neurogenesis appears to be important for coping with new stressors [196] and for the effects of antidepressant drugs [184]. An S1P increase has been indicated to play a causal role in stress-induced anxiety. The local infusion of S1P into the cerebral ventricles for 7 days via osmotic mini-pumps increased anxiety-related behavior in the EPM test. The increase of S1P in the brain caused a regionally selective decrease in tyrosine hydroxylase expression in the amygdala but not in the cortex. Extracellular-signal regulated kinase (ERK) and phosphoERK expression, which are postsynaptic markers for dopaminergic activity, were not significantly affected in either region [97]. These findings suggest that stress may cause an increase in brain S1P levels, which reduces dopamine synthesis in the amygdala and induces an increase in anxiety-related behavior. Sphingosine kinase 2 (SphK2) is the main isoform of the enzyme in the brain. SphK2$^{-/-}$ mice express significantly less S1P and dihydro-S1P in the hippocampus than wild type controls. The initial fear response and acquisition of contextual fear memory was not altered in SpHK2$^{-/-}$ mice. However, SpHK2$^{-/-}$ mice showed a significantly impaired extinction of the fear memory. These findings suggest that S1P is not required for fear-related behavioral conditioning to neutral stimuli. However, S1P appears to be required for the extinction of conditioned fear [82].

S1P can act intracellularly as an epigenetic regulator of histone deacetylase activity [81]. At the cell membrane, S1P can interact with five G-protein coupled receptors, S1P(1)–S1P(5). The S1P(2) receptor is exclusively expressed in hippocampal pyramidal/granular neurons. Mice lacking this receptor (S1P(2)$^{-/-}$) showed a high rate of spontaneous seizures and cognitive deficits. They also exhibited increased levels of anxiety-related behavior in the EPM [4].

There is indirect evidence for an alteration in brain sphingolipids in depression from studies on the stimulatory α-subunit of the G-protein (Gsα). In response to chronic treatment with antidepressant drugs, Gsα migrates from lipid rafts rich in cholesterol and sphingolipids to non-raft membrane domains. Cell and animal studies have revealed an increased coupling between Gsα and adenylate cyclase following antidepressant treatment [48].

Altogether, these findings suggest that sphingolipids in the brain directly control depression/anxiety-related behavior. Although a crucial role for sphingolipids in behavior has only started to emerge, mechanisms of action point toward a modification of monoaminergic receptor signaling and transmitter synthesis.

5.2. Clinical evidence

Brain sphingolipids are implicated in storage diseases such as Niemann–Pick or Gaucher disease [183]. The clinical picture of these

storage diseases is heterogeneous, but the fatal end of the diseases is dominated by central nervous system involvement that includes neurodegeneration. Depression occurs frequently in patients with sphingolipid storage diseases such as Tay–Sachs [128], Fabry [35,117,182] and Gaucher diseases [162].

The quantification of lipids in human brain tissue provides direct evidence for the involvement of sphingolipids in affective disorders. Increased levels of Cer have been found in the white matter of patients with bipolar disorder [187]. Indirect evidence has been obtained from the study of processes in the brain that depend on sphingolipids and from studies using peripheral samples. In the human brain tissue, Gsα is localized to both lipid rafts and non-raft membrane regions. However, in depressed suicide subjects, Gsα is preferentially localized to lipid rafts in the cerebellum and prefrontal cortex [48]. This observation may serve as indirect and circumstantial evidence for an alteration of sphingolipids in the brains of depressed patients. Several studies have used peripheral samples to provide evidence for an altered sphingolipid metabolism in patients with depressive disorders. ASM activity is increased in the peripheral blood mononuclear cells of patients with major depressive disorder with a higher activity in patients with severe symptoms [109]. In a study on cognitively impaired patients and controls, elevated plasma Cer levels have been found in patients with a diagnosis of major depression regardless of dementia status [76]. Elevated ASM activity and Cer levels have been found in the blood of combat veterans with post-traumatic stress disorder [83], which is frequently associated with depression. In Parkinson's disease patients, several Cer species in the plasma were positively associated with depressive symptoms [144]. Altered sphingolipid metabolism has also been found to be associated with depressive symptoms in a Dutch family study [46]. Therefore, all studies investigating peripheral sphingolipid metabolism in patients with depressive symptoms have found an increased activity of ASM and/or elevated levels of Cer. However, the clinical data on the association between depression and sphingolipid metabolism remains insufficient. Two of these studies examined sphingolipid metabolism in patients with major depressive disorder [76,109]. Other studies examined persons with other types of disorders that also had depressive symptoms [46,83,144]. All of these studies used peripheral samples from patients. However, it is likely that sphingolipid metabolism is also altered in the brains of patients with depression. Cer may be the missing link unifying the diverse findings (reduced neurogenesis, increased cardiovascular risk and increased markers of inflammation and oxidative stress) associated with major depressive disorder [111].

6. Summary

Neuronal membranes in the brain are formed by a plethora of lipid species. Neuronal membranes are not fixed structures but show a highly dynamic regulation of their lipid composition. The lipid composition, in turn, may directly control the assembly of signaling proteins in these membranes. This assembly has significant effects on neuronal function and signaling. For example, the membrane lipid composition changes in response to a long-term diet or as a consequence of the complex network of lipid-regulating enzymes. Both sources may contribute to functional behavioral adaptations but may also function as pathways for the pathogenesis of mental disorders. Accumulating evidence now provides strong support for the view that membrane-forming lipids in the brain can play a crucial role in depression and anxiety disorders.

Unsurprisingly, distinct classes of lipids appear to take on different roles in mental disorders. Well-supported preclinical evidence has shown that a lack of n-3 PUFAs in the brain for long periods of time can induce depression- and anxiety-associated behaviors. Functional analyses have suggested that subsequent focal dopaminergic and serotonergic adaptations may mediate these effects. However, numerous other downstream pathomechanisms have been suggested and need confirmation in future studies. Given the omnipresent distribution of membrane lipids at synapses in the brain, we speculate that many more transmitter systems are affected by membrane lipid dysregulation. An increased n-3 PUFA supply may reduce depression- and anxiety-related behavior in normal organisms and also attenuate them in pathological conditions. Possible mechanisms for these beneficial effects include the increase of hippocampal and amygdala circuit function. Clinical evidence supports the hypothesis that subjects with diagnosed depression could benefit from n-3 PUFA administration.

A role for glycerolipids is emerging in the control of anxiety-related behaviors, whereas glycerophospholipids appear to be important for the therapeutic action of antidepressant drugs. There is now strong evidence for an important role of sphingolipids in both the pathogenesis of depression/anxiety and the action of known antidepressant drugs. In particular, the sphingolipid Cer may be the missing functional link between distinct pathological markers of major depressive disorder such as reduced neurogenesis, increased cardiovascular risk and increased inflammation and oxidative stress. Many clinically effective antidepressants inhibit ASM and thus Cer production in the hippocampus, which could be essential for the therapeutic action of the very same antidepressants.

Although the lipid landscape of the brain is complex and highly dynamic, specific lipid classes now appear to be directly involved in depression and anxiety disorders. This knowledge may provide lipid-based targets for disease prevention and treatment. It should be noted that other membrane-forming lipids in the brain may also be involved in depression and anxiety as well as in other mental disorders.

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