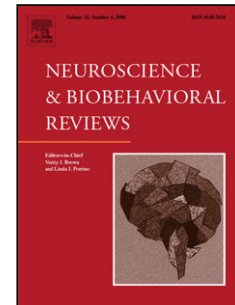


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*Special Issue – IBNS*

## **Lipids in psychiatric disorders and preventive medicine**

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## Highlights

- Lipid systems provide a target for preventive medicine of psychiatric disorders
- We review how brain lipids contribute to major psychiatric disorders
- The focus is on phospholipids/ fatty acids, sphingolipids, and endocannabinoids
- There is a crucial role for brain lipids in depression, schizophrenia, and drug addiction
- Preventive medicine approaches predominantly target life style, diet, and stress

## Abstract

Psychiatric disorders like mood disorders, schizophrenia, or drug addiction affect a sizeable proportion of the human population and severely compromise quality of life. Therefore, measures to prevent the manifestation, and treatments to ameliorate the symptoms, of these disorders are in high demand. Brain lipids determine the localization and function of proteins in the cell membrane of neurons. Lipids may also act as neurotransmitters or other signalling molecules. The lipid composition of the brain can be influenced by nutrition, environmental factors, and by behavioural activity. Thus, lipids represent a target for preventive medicine of psychiatric disorders. Here we review how brain lipids contribute to normal behaviour and to major psychiatric disorders with the focus on phospholipids/ fatty acids, sphingolipids, and endocannabinoids. Accumulating evidence suggests a crucial role for membrane forming and signalling lipids in the brain in the etiopathologies of depression, bipolar disorders, schizophrenia, and drug addiction. Lipids also represent potential preventive interventions for these psychiatric disorders by either targeted dietary supplementation or pharmacological manipulation of lipid regulating enzymes.

## Abbreviations

AA, arachidonic acid (20:4n-6); ABHD,  $\alpha,\beta$ -hydrolase; AC, acid ceramidase; AEA, *N*-arachidonoyl ethanolamide; 2-AG, 2-arachidonoylglycerol; AD, Alzheimer's disease; ALA,  $\alpha$ -linolenic acid (18:3n-3); ASM, acid sphingomyelinase; AMPA, alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; BDNF, brain-derived neurotrophic factor; CBD, cannabidiol; CB1R, cannabinoid receptor type 1; CB2R, cannabinoid receptor type 2; CerS, ceramide synthase; CNS, central nervous system; COX, cyclooxygenase; CPT1C, carnitine palmitoyltransferase 1C; CREB, cAMP response element binding protein; CSF, cerebrospinal fluid; DAG, diacylglycerol; DEA, *N*-docosatetraenoyl ethanolamine; DHA, docosahexaenoic acid (22:6n-3); DPA, docosapentaenoic acid (22:5n-6); eCB, endocannabinoid; EFA,  $\alpha$ -linolenic acid (18:3n-3); EPA, eicosapentaenoic acid (20:5n-3); ERK, extracellular-signal regulated kinase; FAAH, fatty acid amide hydrolase; GalCer, galactosylceramide; GluCer, glucosylceramide; GPCR; G-protein-coupled receptors; HEA *N*-homo- $\gamma$ -linolenoyl ethanolamine; HPA, hypothalamic-pituitary-adrenal; 5-HT, serotonin; IFN $\alpha$ , interferon- $\alpha$ ; LacCer, lactosylceramide; MAGL, monoacylglycerol lipase; MCI, mild cognitive impairment; MR, magnet resonance; Nacc, nucleus accumbens; NADA, *N*-arachidonoyl-dopamine; NAPE-PLD *N*-acylphosphatidylethanolamine-specific phospholipase D; NArPE, *N*-arachidonoylphosphatidyl-ethanolamines; NC, neutral ceramidase; NMDA, *N*-methyl-D-aspartate, NSM, neutral sphingomyelinase; OEA, oleoyl ethanolamide; PC, glycerophosphocholine; pCPA, *p*-chlorophenylalanine; PCP, phencyclidine; PE, phosphatidylethanolamine; PEA, palmitoyl ethanolamide; PFC, prefrontal cortex; PI, phosphatidylinositol; PLC, phospholipase C; PPAR, peroxisome proliferator-activated receptor; PUFA, polyunsaturated fatty acid; SNP, single nucleotide polymorphism; S1R, sigma 1 receptor; Sph, sphingosine; S1P, sphingosine-1-phosphate; SphK2, sphingosine kinase 2; SPT-1, serine palmitoyl transferase 1; THC,  $\Delta$ 9-tetrahydrocannabinol; TRPV1, transient receptor potential vanilloid receptor type 1; VMAT2, vesicular monoamine transporter2; VTA, ventral tegmental area.

**Keywords:** phospholipids, fatty acids, sphingolipids, endocannabinoids, depression, anxiety, schizophrenia, addiction

## 1. Introduction

Mental function in mammals involves the sensation and perception of sensory stimuli, analysis of perceived information, and subjective emotional and behavioural responses to the perceived stimuli and information. It also includes how information is processed by cognitive activity, how it is stored in memory systems, and how it is retrieved on demand. Together, these processes determine how an organism perceives itself and how it interacts with its environment and conspecifics. Deviation in one or more dimension of mental activity from what is perceived as 'normal' constitutes psychological disturbances and psychiatric disorders (Schumann et al., 2014). The anatomical substrate of mental activity is the brain, which operates in close interaction with all other organs of the body (O'Mahony et al., 2015). As in peripheral organs, function of the brain depends on nutrient supply. Over time, even small changes in nutrition may affect microstructure and activity of the brain in various ways. This may eventually affect functions as complex as 'personality', in keeping with the proverbial consequence of "Du bist, was Du isst" (you are what you eat; Ludwig Feuerbach). Thus, nutrition contributes not only to physical well-being, but also mental health; whereas malnutrition, which is essentially defined by its consequences, can contribute to mental illness. In contrast, there are certain diets that may counteract and even reverse psychiatric problems induced by other factors, such as stress (Bergouignan et al., 2009).

A major class of molecules that fundamentally determine cell function in the brain are lipids. Lipids and/or their precursors derived from food are taken up by the organism and used for the maintenance of general cell function. In particular, the integrity of cell membranes and signalling through membranes depend on lipid homeostasis in the brain. Studies published in recent years have provided new insights into how lipid homeostasis, most notably of phospholipids, sphingolipids, and endocannabinoid

lipids, affects mental functions. These findings serve as the basis for a preventive medicine approach for psychiatric disorders by which the risk for developing psychiatric disorders may be mitigated by interventions that modulate lipid homeostasis in the brain. Evidence supporting this approach is reviewed here.

## **2. Targeting psychiatric disorders by preventive medicine**

### **2.1. What is preventive medicine and its application in psychiatric disorders**

A number of serious psychiatric disorders tend to emerge during critical neurodevelopmental periods, such as adolescence, and often lead to protracted illness phases with significantly reduced quality of life. Efforts aimed at the prevention of mental disorders include reducing incidence, prevalence, and preventing or delaying recurrence; limiting the duration of symptoms; and decreasing the impact of illness in the affected person, their families and society (Mrazek and Haggerty, 1994). Prevention is important when aiming to successfully reduce the prevalence of a disease (Barrera et al., 2007; Munoz et al., 2010).

### **2.2. Major brain lipids and how to manipulate them**

Findings from animal experiments demonstrate that brain lipids can be manipulated via multiple paths and mechanisms, but does this also apply to the human brain, and if so, how can the brain lipids be examined in humans? A proxy is the estimation of the effects of nutritional manipulations on brain lipids via neurological, psychiatric, or ophthalmological read-outs (Uauy et al., 2001). In humans, postmortem examination allows the direct analysis of lipids and their associated enzymes in the brain (O'Brien and Sampson, 1965; Spence et al., 1979; Söderberg et al., 1990; Svennerholm et al., 1994). Individual lipids can be quantified to a limited extent with in vivo magnet resonance (MR) spectroscopy (Kwee and Nakada, 1988; Pettegrew et al., 1991;

Manganas et al., 2007). In fact, a marker for neural progenitor cells of the hippocampus, which is most likely composed of a mixture of saturated and unsaturated fatty acids, has been described using in vivo MR spectroscopy. This marker is detected in high abundance in the hippocampus and in the cortex and decreases with increasing age (Manganas et al., 2007). Analysis of brain lipids and associated enzymes in cerebrospinal fluid (CSF) can also be used as an indirect assessment of brain lipid status (Mulder et al., 1998; Fonteh et al., 2006; Kosicek et al., 2012; Mühle et al., 2013).

Brain lipids are subject to natural and physiological influences such as age, sex, sleep, but are also influenced by disease processes such as HIV dementia, Huntington's disease, Alzheimer's disease (AD), or schizophrenia (Pettegrew et al., 1991; Gattaz et al., 1996; Mulder et al., 1998; Yao et al., 2000; Han et al., 2002; Haughey et al., 2004; Desplats et al., 2007). Regardless of physiological fluctuations or disease processes, the lipids in the brain can be actively manipulated. Small molecules, such as drugs that cross the blood-brain barrier may alter the lipid metabolism in the brain. These include functional inhibitors of acid sphingomyelinase (Kornhuber et al., 2010), phospholipidosis-inducing drugs (Mühlbacher et al., 2012), inhibitors of fatty acid synthase (Loftus et al., 2000), or inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A reductase (statins; Botti et al., 1991; Fassbender et al., 2002; Locatelli et al., 2002). Another way to manipulate brain lipids is the intravenous or intracisternal administration of lipid metabolizing enzymes (enzyme replacement therapy), which is used primarily in the treatment of lipid storage diseases. Dietary intake of specific fatty acids, notably n-3 polyunsaturated fatty acids (PUFAs), also alters the levels of certain lipids in the brain and can affect human brain function, as measured by indirect parameters (Eilander et al., 2007). Taken together, brain lipids can be targeted by drugs, enzyme replacement therapy, gene therapy, or dietary

manipulations; however, most data on these approaches come from preclinical studies. Data on the effects of these treatments in humans is still limited and further studies are needed.

### 2.2.1 Fatty acids and phospholipids

Polyunsaturated fatty acids are fatty acids containing multiple double bonds. Long chain PUFAs, which are more than 20 carbons in length, are derived from two independent and nutritionally essential fatty acids (EFA),  $\alpha$ -linolenic acid (18:3n-3) and linoleic acid (18:2n-6; Fig. 1). The n-3 or n-6 designation (or *omega*-3 or *omega*-6) indicates the presence of double bond at the third or sixth carbon bond, respectively, from the methyl end of the hydrocarbon chain. Mammals cannot introduce a double bond in the n-3 or n-6 position of the fatty acid chain, and thus, must obtain  $\alpha$ -linolenic acid and linoleic acid from the diet. However, mammals can elongate the EFAs into biologically important n-3 and n-6 PUFAs such as eicosapentaenoic acid (EPA; 20:5n-3), docosahexaenoic acid (DHA; 22:6n-3), and arachidonic acid (20:4n-6). The relative abundance of these PUFA depends on the dietary intake of the EFAs or the PUFAs themselves (Fenton et al., 1999; Nakamura et al., 2001).

Long chain PUFAs, as well as other fatty acids, are components of the phospholipids that form the membranes of all cells, including neurons. Within the membrane lipid bilayer, phospholipids that contain PUFAs are preferentially localized around membrane proteins (Fenton et al., 1999; Uauy et al., 2000). As such, variation in the PUFA composition of synaptic membranes alters the microenvironment, and thus structure and function, of membrane-bound proteins such as receptors and ion channels (Salem et al., 2001), and thus affects neuronal function. N-3 and n-6 PUFAs can also be cleaved from the cell membrane by phospholipases, such as



phospholipase A<sub>2</sub>. Free fatty acids modulate gene expression at the transcriptional level through the activation of transcription factors (e.g., PPAR, LXR, and RXR) (Khan and Vanden Heuvel, 2003), and can also be metabolized into inter- and intracellular signalling substances, such as prostaglandins, thromboxanes, resolvins, maresins, and protectins (Bannenberg, 2010; Bazan, 2005; Horrocks and Farooqui, 2004; Salem et al., 2001; Serhan and Petasis, 2011).

In animal models, the most common method of manipulating the relative amounts of n-3 and n-6 PUFAs in brain phospholipids, as well as the concentrations of free fatty acids, is by altering the n-3 and n-6 PUFA content of the diet. A diet low in  $\alpha$ -linolenic acid (ALA; 18:3n-3), the essential fatty acid precursor of DHA, results in decreased concentrations of DHA in brain phospholipids accompanied by increased incorporation of the 22-carbon n-6 PUFA docosapentaenoic acid (DPA; 22:5n-6; Favreliere et al. 1998; Galli et al., 1971). Increased levels of arachidonic acid (AA; 20:4n-6) are also sometimes reported after treatment with n-3 PUFA-deficient diets (Bondi et al. 2014; McNamara et al., 2008). Alternatively, diets high in DHA increase phospholipid DHA content in the brain (Barcelo-Coblijn et al., 2003; Favreliere et al., 2003). The duration of treatment required to significantly alter brain phospholipid composition depends on the developmental stage of the animal. For example, because DHA accumulates in the brain primarily during the late prenatal and early postnatal periods (Clandinin et al., 1980a, 1980b; Green and Yavin, 1996), dietary manipulations of the pregnant and nursing dam or the neonate can readily alter fatty acid composition of brain phospholipids of the pups. In contrast, once DHA has accumulated in the brain, the composition of brain phospholipids tends to remain fairly consistent. Accordingly, feeding adult male rats an n-3 PUFA-deficient diet for 7 months did not decrease brain DHA content (Bourre et al., 1992). However, studies in adult female rats and adult male mice have since shown that diets low in n-3

PUFAs can decrease in the percentage of DHA of the adult brain, but very slowly. This is consistent with rate of fatty acid turnover in that tissue, which is normally slow and decreases further under conditions of low n-3 PUFA availability (DeMar et al., 2004; Levant et al., 2006b; McNamara et al., 2008).

A less common approach to manipulating brain phospholipid and free PUFA composition experimentally is the use of transgenic animals, such as the *fat-1* mouse that express *C. elegans fat-1*, an enzyme capable of metabolizing n-6 PUFAs into n-3 PUFAs (Kang et al., 2004). Using this approach, feeding an n-3 PUFA-deficient diet to *fat-1* and control mice resulted in animals with and without adequate n-3 PUFAs.

Physiological processes can also change tissue phospholipid fatty acid composition. Most notably, the delivery of DHA to the developing foetus and neonate during pregnancy and lactation results in dramatic decreases in the DHA content of the maternal liver and erythrocytes, even when the dam is fed a presumably adequate diet (Levant et al., 2006b, 2007). Brain PUFA composition does not change if the dam is fed an adequate diet. However, when the diet contains inadequate n-3 PUFAs, diet and physiological status interact to decrease brain DHA rapidly (Levant et al., 2006b; Levant et al., 2006d).

### 2.2.2. Sphingolipids

Mammalian cell membranes are predominantly composed of sphingolipids, cholesterol and (glycero)phospholipids. In 1972, Singer and Nicolson suggested the fluid mosaic model of the cell membrane based on biophysical experiments measuring the melting temperatures of lipids in biological membranes. This model predicted that lipids are present in the membrane in a liquid disordered phase with free movement of proteins in the lipid bilayer (Singer and Nicholson, 1972). . This

view has changed in the last 20 years: In particular sphingolipids and cholesterol do not seem to be randomly distributed in the membrane. Sphingolipids are composed of a hydrophilic head group and a hydrophobic ceramide molecule. Ceramides are composed of D-erythro-sphingosine and a fatty acid containing 2-36 carbon atoms in the acyl chain (C2-C36 ceramide species; Sandhoff, 2010). The amino alcohol and the fatty acid form an amide ester. Sphingolipids tend to interact with each other through interactions of the hydrophilic sphingolipid head groups (Simons and Ikonen, 1997; Harder and Simons, 1997; Brown and London, 1998; Xu et al., 2001; London and London, 2004; Megha et al., 2006). However, since the head groups are rather bulky, these interactions need to be coordinated in order to prevent steric hindering. This coordination is mediated by cholesterol, which interacts with sphingolipids, particularly the most abundant sphingolipid sphingomyelin, via hydrophobic van der Waal interactions of its sterol ring with the ceramide part of sphingolipids, as well as hydrogen bonds of the hydroxy-group in the cholesterol molecule with the polar head group of sphingolipids (Brown and London, 1998; Xu et al., 2001; London and London, 2004; Megha et al., 2006). The coordinated interaction of sphingolipids with cholesterol results in an ordered membrane structure with cholesterol filling the voids between the bulky sphingolipids. Due to the tight interactions between sphingolipids and cholesterol, stable domains are formed that exist in a liquid-ordered- or even gel-like phase (Simons and Ikonen, 1997; Harder and Simons, 1997; Brown and London, 1998; Xu et al., 2001; London and London, 2004; Megha et al., 2006). These domains spontaneously separate from other phospholipids in the cell membrane. Since they float in the membrane, these very small domains were named lipid rafts (Simons and Ikonen, 1997). The introduction of these lipid rafts in the concept of membrane composition indicates a lateral organization of the cell membrane. A microscopy study confirmed the existence of small membrane rafts with a diameter of

20 nm (Eggeling et al., 2009). It should be noted that lipid rafts were only demonstrated in the outer leaflet of the plasma membrane, while it is unknown whether lipid rafts or similar membrane domains exist in the inner/cytoplasmic leaflet of the plasma membrane.

Sphingomyelin can be hydrolyzed to ceramide (Fig. 2). The generation of ceramide within lipid rafts, or in general in the membrane (even outside of rafts), dramatically alters the biophysical properties of the plasma membrane and presumably also intracellular membrane: Ceramide molecules have the tendency to spontaneously self-associate, a process that results in the formation of ceramide-enriched membrane microdomains that further fuse to large ceramide-enriched macrodomains, which can be easily detected by fluorescence microscopy (Veiga et al., 1999; Holopainen et al., 1998; Grassmé et al., 2001a). It is very likely that these domains exist in a gel-like phase, are very hydrophobic, and also alter the diameter of the membrane. Ceramide molecules within these domains appear to be tightly packed and, therefore, seem to stabilize lipid rafts (Xu et al., 2001; London and London, 2004). Ceramide-enriched membrane platforms were visualized by confocal microscopy *in vivo* in non-fixed cells or after fixation using fluorescent-labelled anti-ceramide antibodies (Grassmé et al., 2001a, 2001b, 2002a, 2002b; Dumitru and Gulbins, 2006; Abdel Shakor et al., 2004; Lacour et al., 2004; Fanzo et al., 2003). Further biophysical studies were able to follow the formation of ceramide-enriched membrane macrodomains on line by treatment of phosphatidylcholine/sphingomyelin-unilamellar vesicles with sphingomyelinase immobilized onto a microbead and applied via a glass pipette to the surface of the vesicle (Holopainen et al., 1998).

The generation of ceramide within extracellularly-oriented lipid rafts/membrane domains, i.e. in the outer leaflet of the plasma membrane on the cell surface, is

mediated by the enzyme acid sphingomyelinase (ASM; Grassmé et al., 2001a), which belongs to the family of sphingomyelinases that hydrolyse sphingomyelin to ceramide (Henry et al., 2013). Depending on the optimal pH for enzyme activity, an acid and several neutral and alkaline sphingomyelinase have been identified (Henry et al., 2013). Ceramide can be also generated in membranes de novo by ceramide synthases, which also determine the chain length of the fatty acid in the ceramide molecule (Tidhar and Futerman, 2013). In addition, ceramide can be generated by hydrolysis of glycosylated sphingolipids (Ishibashi et al., 2007) and retrograde activity of the enzyme ceramidase triggering the formation of ceramide from sphingosine (Sph; Okino et al., 2003), although it is unknown whether these pathways are active in lipid rafts (Fig. 2).

Our and other's findings demonstrate that ASM is activated and ceramide release is triggered by stimulation via CD95 (Grassmé et al., 2001a, 2001b), CD40 (Grassmé et al., 2002a), DR5 (Dumitru and Gulbins, 2006), Fc $\gamma$ RII (Abdel Shakor et al., 2004), the PAF-receptor (Goggel et al., 2004), CD14 (Pfeiffer et al., 2001), integrins (Carpinteiro et al., 2015); after infection with *P. aeruginosa* (Grassmé et al., 2003), *S. aureus* (Esen et al., 2001), *N. gonorrhoeae* and *meningitidis* (Grassmé et al., 1997; Hauck et al., 2000, Simonis et al., 2014), rhinovirus (Grassmé et al., 2005); application of stress stimuli such as  $\gamma$ -irradiation (Santana et al., 1996), UV-light (Charruyer et al., 2005; Zhang et al., 2001; Rotolo et al., 2005; Kashkar et al., 2005), cisplatin (Lacour et al., 2004) or Cu<sup>2+</sup>-treatment (Lang et al., 2007); and even in some conditions of developmental death (Scheel-Toellner et al., 2004). It is surprising that a simple change of the biophysical properties of the plasma membrane seems to be involved in such a variety of signalling pathways that have at least partially different biological effects. This general function of ceramide might be explained by the phenomenon of receptor trapping/clustering within ceramide-enriched membrane domains. It was

previously demonstrated that stimulation of CD95, DR5 or CD40 induces a trapping and clustering of the receptor molecules in ceramide-enriched membrane platforms (Grassmé et al., 2001a, 2001b, 2002a; Dumitru and Gulbins, 2006). The generation of a very high concentration of a receptor within a small domain of the plasma membrane seems to be prerequisite for transmembrane signalling via the clustered receptors (Gulbins and Kolesnick, 2003). Clustering of receptors may not only result in a very high receptor density, but also a novel spatial distribution of the receptor in the plasma membrane. It may also facilitate association of activated receptors with downstream signalling molecules and transactivation of enzymes associating with the activated receptor, exclude inhibitory molecules, and stabilize the interaction of the cognate receptor with its ligand. Thus, ceramide-enriched membrane platforms may have a very general function in signal transduction, i.e. the re-organization of receptors and signalling molecules in and at the cell membrane to facilitate and amplify signalling processes via a specific receptor.

Utilizing the observation that CD40 clusters in ceramide-enriched membrane domains while CD45 does not, chimeric constructs of CD40 and CD45 have been used to study the molecular mechanisms that mediate receptor clustering, (Cheng et al., 1999). These studies revealed that the transmembrane domain of CD40 determines receptor clustering, however, molecular details still require definition (Bock and Gulbins, 2003).

Sphingolipids are present in all eukaryotic cells and can therefore serve as bioactive food components (Vesper et al., 1999). Cellular sphingolipid metabolism and action can be altered by dietary sphingolipids, but also by other food components. In mice, a high fat diet leads to increased ceramide levels and enhanced ASM or neutral sphingomyelinase (NSM) expression and activity in plasma, adipose tissue, liver, and the hypothalamus (Boini et al., 2010; Chocian et al., 2010; Borg et al., 2012).

Furthermore, free fatty acids increase ceramide formation in cultured pancreatic cells (Shimabukuro et al., 1998). Dietary intake of n-3 PUFAs reduces the production of ceramide in splenic lymphocyte cultures (Jolly et al., 1999) and in the skeletal muscle of mice (Lanza et al., 2013), and also reduces hippocampal ceramide levels (Babenko and Semenova, 2010). Consistent with these preclinical observations, randomized control studies in humans also found that enhanced dietary levels of n-3 PUFAs reduced ceramide levels in the serum and muscle (Lankionen et al., 2009; Kien et al., 2013).

There is a complex link between cholesterol, sphingolipid metabolism, and function. In rats, a cholesterol rich diet increases ceramide abundance in the plasma and adipose tissue (Ichi et al., 2007). This diet results in accumulation of cholesterol, sphingomyelin, and galactosylceramide (GalCer) and increases lipid peroxidation products in the hippocampus (Stranahan et al., 2011). Soy protein consumption can reduce the ceramide content of the heart, probably by reducing the expression of serine palmitoyl transferase1 (SPT-1), a key enzyme in the formation of ceramide (Torre-Villalvazo et al., 2009). Alcohol enhances the activity of ASM and results in increased ceramide levels in cell culture (Pascual et al., 2003; Saito et al., 2005), rodent models (Saito et al., 2010; Liangpunsakul et al., 2012), and humans (Reichel et al., 2010, 2012).

There have been mixed results with the effects of physical activity on tissue ceramide abundance in rodents (Dobrzyn et al., 2004; Helge et al., 2004; Baranowski et al., 2008; Blachnio-Zabielska et al., 2008; Tsalouhidou et al., 2009; Jung and Kang, 2010; Borg et al., 2012). A randomized control study found decreased skeletal muscle ceramide levels after exercise in humans (Dube et al., 2011).

Ageing is associated with changes in brain sphingolipid levels and catabolic enzyme activity. A decline in sphingomyelin levels in the hippocampus of aging rats was

reported by Babenko and Semenova (2010). A recent study, however, did not find ageing-associated changes in sphingomyelin species in the hippocampus and cerebellum of rats (Huston et al., 2016); however, total ceramide levels were reduced in aged animals, specifically in the dorsal hippocampus. Aged animals also exhibited significantly higher ASM activity in this brain area and in the cerebellum compared to adult rats (Huston et al., 2016), similar to findings from whole brain homogenates (Sacket et al., 2009). In rats, increased age was associated with enhanced NSM, but not ASM activity and subsequent ceramide accumulation in the brain (Babenko and Shakhova, 2014; Huston et al., 2016). Caloric restriction or treatment with N-acetylcysteine or  $\alpha$ -tocopherol acetate reduced NSM activity and hippocampal ceramide content (Babenko and Shakhova, 2014). No age effects were found on acid ceramidase (AC) or neutral ceramidase (NC) activity in the hippocampus and cerebellum. However, another study found an increase in both enzyme activities during aging in whole brain homogenates (Sacket et al., 2009).

The exact role of diet in brain sphingolipid metabolism and ceramide abundance is not completely understood. From the limited information available, a healthy lifestyle with a diet high in n-3 PUFAs and antioxidants, and low in free fatty acids, cholesterol (e.g., the Mediterranean diet), and physical activity might contribute to a reduced ceramide load (Bergouignan et al., 2009); however, the effects of lifestyle on ceramide load have been investigated in only a few randomized control studies in humans (Lankinen et al., 2009; Dube et al., 2011; Kien et al., 2013).

### **2.2.3. Endocannabinoids**

The endocannabinoid (eCB) signalling system consists of the G-protein coupled cannabinoid receptors (CB1R and CB2R), the two main endogenous ligands *N*-arachidonylethanolamide (anandamide, AEA) and 2-arachidonoylglycerol (2-AG),



and their synthetic and metabolic enzymes. This evolutionarily ancient and widely distributed neuromodulatory system is crucial for sustaining and restoring homeostasis of neurotransmission in various different central and peripheral processes. Thus, it participates in a multitude of neurophysiological processes such as reward-related behaviours, pain perception, emotional homeostasis, cognition, or motor control (Elphick 2012; Kano et al., 2009). CB1R and CB2R are also the main molecular targets for exogenous cannabinoids, such as plant derived phytocannabinoids from *Cannabis sativa* (e.g.  $\Delta^9$ -tetrahydrocannabinol) and hence mediate the pharmacological effects of cannabis use/abuse. Other compounds that were recently discussed as putative endogenous ligands include noladin ether (2-arachidonyl-glycerol-ether) that binds to and activates CB1R, virodhamine (O-arachidonoyl-ethanolamine), the ester of arachidonic acid and ethanolamine, and the endogenous vanilloid agonist, N-arachidonoyl-dopamine (NADA), which also exhibits affinity for CBR in vitro, and finally N-homo- $\gamma$ -linolenylethanolamine (HEA) and N-docosatetraenylethanolamine (DEA) (for review see: Piomelli, 2003; Buczynski and Parsons, 2010). Notably, the N-acyl ethanolamines palmitoylethanolamide (PEA) and oleoylethanolamide (OEA) are receiving increasing interest as potential endocannabinoids, although they appear not to interact with the classical CBR (for review see: Buczynski and Parsons, 2010). However, the presence of most of these compounds in intact tissues is still a matter of debate and their pharmacological activity and metabolism still needs to be characterized in detail. Therefore, AEA and 2-AG are still considered the primary endogenous mediators of eCB signalling (Buczynski and Parsons, 2010). Beyond the role of cannabis use/abuse as a risk factor for the emergence of major psychiatric disorders, growing evidence implicates alterations in the eCB system - independent from cannabis ingestion - in the etiology

and pathophysiology of various neuropsychiatric disorders (Leweke and Koethe, 2008; Marco et al., 2011; Rubino et al., 2015).

The main endogenous ligands of both CBR are the endocannabinoids AEA and 2-AG. AEA acts as a partial agonist on both CBRs and as a full agonist at the vanilloid receptor, TRPV1 (transient receptor potential vanilloid receptor type). 2-AG acts as a full agonist for CB1R and CB2R (Kano et al., 2009; Castillo et al., 2012). eCBs cannot be stored in vesicles due to their lipophilic nature. They are synthesized on demand in an activity-dependent manner in response to elevation of intracellular calcium levels. Both AEA and 2-AG are derivatives of arachidonic acid and bind with different affinities and efficacies to CB1R and CB2R, where they produce effects of short duration due to rapid metabolic inactivation. Both eCBs are rapidly degraded by the two main hydrolytic enzymes, fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL). Hence, eCB levels can be manipulated mainly by indirect strategies, where inhibiting the cellular uptake or intracellular metabolism of eCBs following their endogenous release increases the interstitial concentrations of AEA and 2-AG (Pertwee, 2008; Kano et al., 2009; Pertwee, 2014).

2-AG is synthesized from the hydrolysis of 2-arachidonoyl-containing diacylglycerols (DAG) by either of two enzymes known as sn-1-specific DAGL  $\alpha$  or  $\beta$  (Fig. 3). Notably, studies employing DAGL $\alpha$ - and DAGL $\beta$  knockout mice indicate that the contribution of DAGL $\beta$  to 2-AG biosynthesis in the adult brain is much less significant than DAGL $\alpha$  (Iannotti et al., 2016; Elphick 2012). The mechanisms by which AEA is synthesized in vivo in the brain are not yet fully understood, although multiple, and potentially interacting, pathways might be involved. At least three putative biosynthesis pathways have been suggested so far: 1.) the direct synthesis of AEA by hydrolysis of N-arachidonoylphosphatidyl-ethanolamines (NArPE) by N-acylphosphatidylethanolamine-specific phospholipase D (NAPE-PLD), 2.) by

sequential deacylation of NArPE by the  $\alpha\beta$  hydrolase 4 (ABHD4) and hydrolysis of glycerophosphoethanolamine by the glycerophosphodiesterase GDE1, and 3.) via a phospholipase C (PLC)-like enzyme mediated hydrolysis of NArPEs to phosphoanandamide, followed by dephosphorylated to AEA by a phosphatase, such as tyrosine phosphatase PTPN22 (Fig. 3). Studies using knockout mice further indicate that inhibition of one of these pathways in the brain can potentially be compensated for by the remaining biosynthesis routes (Iannotti et al., 2016; Elphick 2012; Blankman and Cravatt, 2013).

FAAH is a major metabolising enzyme of AEA, but can also metabolise 2-AG. MAGL is thought to be largely, but not exclusively responsible for the metabolism of 2-AG. Notably, both eCBs can also be metabolised to varying extents by other enzymes (AEA: N-acyl ethanolamine hydrolysing acid amidase; 2-AG: MAG kinase,  $\alpha,\beta$ -hydrolase (ABHD)6 and ABHD12; AEA & 2-AG: cytochrome P450 enzymes, lipoxygenases and cyclooxygenase (COX)-2) (Pertwee, 2014; Kano et al., 2009; Blankman and Cravatt, 2013). FAAH inhibitors include irreversible inhibitors such as URB597 and O-1887 and the reversible inhibitor OL135. In rodents, URB597 was shown to elevate brain AEA levels without altering 2-AG levels. URB597 was, therefore, used to probe AEA-regulated physiology in vivo. Additional examples of the many FAAH inhibitors that have recently been developed include URB532, URB694, AM374 (palmitylsulphonyl fluoride), N-arachidonoyl glycine, N-arachidonoyl serotonin, JNJ1661010, CAY10401(13), AM3506, AM5206, ST4070, PF3845, and PF04457845. MAGL inhibitors include the non-competitive/irreversible inhibitors, URB602, JZL184 and N-Arachidonoyl maleimide and the reversible inhibitor, OMDM169. Very recently, a next-generation MAGL inhibitor (KML29) based on an O-hexafluoroisopropyl carbamate scaffold has been developed that possesses superior selectivity toward MAGL.

Notably, only dual FAAH/MAGL inhibitors (e.g. JZL195, SA-57) closely resemble effects that are produced by direct CBR agonists. Unlike JZL195, which displays similar potency toward FAAH, MAGL, and ABHD6, SA-57 is considerably more active toward FAAH and was found to selectively inhibit FAAH at low doses, and to cross-react with MAGL and ABHD6 at higher doses in mice. This selectivity profile allows SA-57 to act simultaneously as a complete FAAH inhibitor and partial MAGL/ABHD6 inhibitor *in vivo* (for detailed review see: Pertwee, 2014; Blankman and Cravatt, 2013).

Aside from these indirect pharmacological modulations, another approach to experimentally manipulate eCB levels in the brain is the generation of mice with a genetic deletion of FAAH or MAGL. Generation and characterization of mice bearing targeted disruption of the *Faah* gene (FAAH(–/–) mice) confirmed FAAH's role as the principal AEA hydrolase *in vivo* (Cravatt et al., 2001). FAAH(–/–) mice are viable, fertile, and largely indistinguishable from wild-type littermates. Brains from FAAH(–/–) mice have been found to exhibit dramatically elevated (>10-fold) AEA levels, while 2-AG levels and CB1R expression remain unchanged (Cravatt et al., 2001; Blankman and Cravatt, 2013). Mouse models bearing genetic disruption of the *Mgl1* gene (MAGL(–/–) mice) have also been described (Chanda et al., 2010; Schlosburg et al., 2010). These animals display dramatic reductions in 2-AG hydrolase activity and elevations in 2-AG and other MAGs in the brain and many peripheral tissues (Blankman and Cravatt, 2013).

### **3. Lipids in mood and anxiety disorders**

#### **3.1. Fatty acids and phospholipids**

*Preclinical findings:* N-3 PUFAs affect a number of the neurobiological mediators believed to be involved in the pathophysiology of depression. Findings vary due to

the wide range of animals models used, which differ in the magnitude of the changes in brain phospholipid composition as well and the point in the lifespan when that change occurred. Nevertheless, these studies point to the influence of PUFAs on systems regulating mood (Müller et al., 2015).

Consistent with the reduced concentrations of serotonin (5-HT) found postmortem in the brains of depressed patients and individuals dying by suicide (Beskow et al., 1976; Lloyd et al., 1974; Shaw et al., 1967), brain levels of 5-HT and its biosynthetic enzyme tryptophan hydroxylase were lower in animals with diet-induced decreases in brain DHA content (Levant et al., 2008; McNamara et al., 2009a; McNamara et al., 2010a). Consistent with a role for DHA in the regulation of 5-HT levels, treatments that increase brain DHA content resulted in higher 5-HT concentrations (Carabelli et al., 2014; Sugasini and Lokesh, 2014; Vines et al., 2011, 2012), and reversed the reduced 5-HT levels induced by chronic unpredictable mild stress (Vancassel et al., 2008). In addition, rats with a reduction of brain DHA levels of about 70% resulting from feeding a n-3 PUFA-deficient diet for two generations, had higher density of cortical 5-HT<sub>2A</sub> receptors (Delion et al., 1994, 1996), similar to that observed postmortem in depressives or individuals dying by suicide (Arango et al., 1990).

The mesolimbic dopamine system, which when hypofunctioning may contribute to the anhedonia observed in depression (Nestler and Carlezon, 2006), is also affected by some treatments that alter brain PUFAs. In agreement with the reduced levels of D2 dopamine receptors or mRNA in the nucleus accumbens (Nacc) of depressed women and in several rat models of the disease (Bjornebekk et al., 2007; Kram et al., 2002; Moses-Kolko et al., 2012; Papp et al., 1994; Yaroslavsky et al., 2006), postpartum female rats with a 25% decrease in brain DHA content resulting from the combined effects of pregnancy, lactation, and n-3 PUFA-deficient diet, had lower densities of D2 receptors in that brain region (Davis et al., 2010).

Manipulations that reduce brain DHA content can produce changes in hypothalamic-pituitary-adrenal (HPA) axis function similar to the dysregulation of this system in depression (Plotsky et al., 1998). Notably, postpartum female rats with a 25% decrease in brain DHA content had elevated stress-induced serum corticosterone levels, as well as greater relative increases in corticosterone secretion over basal levels, compared to postpartum females with normal brain DHA levels (Levant et al., 2008). Conversely, rats fed diets supplemented with n-3 PUFAs for 2-3 months had lower plasma corticosterone levels when subjected to acute stressors (Ferraz et al., 2011; Jiang et al., 2012). Augmented stress responses in n-3 PUFA-deficient animals, and attenuated responses in n-3 PUFA supplemented animals, have also been reported in chronic stress paradigms (Harauma and Moriguchi, 2011; Hennebelle et al., 2012; Mathieu et al., 2008). A recent study suggests that disruption of glucocorticoid receptor signalling in n-3 PUFA-deficiency contributes to these effects (Larrieu et al., 2014).

Similar to the reduced levels of hippocampal brain-derived neurotrophic factor (BDNF) found in depression (Schmidt et al., 2011), expression of BDNF is modulated by treatments that change brain DHA concentrations. In a variety of animal models, treatments that decrease brain DHA result in reduced expression, whereas those that increase brain DHA result in higher expression (Blondeau et al., 2009; Cysneiros et al., 2010; Dwivedi et al., 2003; Ferreira et al., 2013; Karege et al., 2005; Levant et al., 2008; Venna et al., 2009; Vines et al., 2012; Wu et al., 2004). Recent evidence suggests that this regulation of BDNF expression involves DNA methylation (Tyagi et al., 2015). Consistent with those observations, a diet enriched with DHA increased concentrations of the BDNF signalling mediators, calmodulin kinase II and activated Akt, pro-BDNF processing enzymes such as tissue plasminogen activator, and proteins involved of the increases in BDNF induced by antidepressant drugs such as

cAMP response element binding protein (CREB; Park et al., 2012; Tang et al., 2015a; Wu et al., 2007).

Animal behaviours relevant to depression are affected by modulation of brain PUFA composition. Most notably, in the majority of studies, rodents with experimentally-induced increases in brain DHA content exhibited behaviours in tests such as the forced-swim-test and tail-suspension-test that are similar of those produced by antidepressant drugs, whereas treatments that reduce brain DHA have the opposite effect (Blondeau et al., 2009; Carabelli et al., 2014; Chen and Su, 2013; DeMar et al., 2006; Ferraz et al., 2011; Huang et al., 2008; Jiang et al., 2012; Laino et al., 2010; Lakhwani et al., 2007; Moranis et al., 2012; Park et al., 2012; Venna et al., 2009; Vines et al., 2011; Weiser et al., 2015; Wietzych-Schindler et al., 2011). In some studies, treatments involving decreased n-3 PUFAs also resulted in anhedonia (Frances et al., 2000; Papp et al., 1991). Fish oil supplementation reversed depression-like behaviours induced by chronic unpredictable mild stress and treatments that induce depression-like behaviour in rodents (Tang et al., 2015b).

Finally, anxiety, which can occur alone or together with depression, is affected by PUFAs. Rodents fed diets with inadequate n-3 PUFA exhibited behaviours consistent with increased anxiety in behavioural paradigms such as the open field, elevated-plus-maze, and the conditioned fear tests (Bondi et al., 2014; Carrie et al., 2000; Chen and Su, 2011; Takeuchi et al., 2003). Similar effects have been reported in pigs and primates (Clouard et al., 2015; Pifferi et al., 2015).

In addition to findings showing that manipulations of brain fatty acids affect neurobiology in ways that may contribute to mood disorders, preclinical studies also suggest that some drugs used in the treatment of mood disorders, such as bipolar disorder, may act through mechanisms involving brain phospholipids. Notably, AA turnover and expression of cPLA2, the phospholipase selective for AA, in rat brain

were downregulated by clinically-approved drugs (i.e., lithium and carbamazepine) used as mood stabilizing agents for bipolar disorder, suggesting a common mechanism of action in this condition (Rapoport, 2014).

*Human findings:* A number of studies suggest a relationship between depressive symptoms and tissue levels of n-3 PUFAs. Many of the studies of the PUFA composition in the serum, plasma, or erythrocytes, as well as a meta-analysis, indicated lower DHA concentrations, or increased n-6:n-3 PUFA ratio in depression, as well as in anxiety (Assies et al., 2010; Lin et al., 2010; Lotrich et al., 2013; Marx et al., 2015; McNamara et al., 2010b; McNamara et al., 2014; Pottala et al., 2012; Riemer et al.; Swenne et al., 2011; Tsuchimine et al., 2015; Verly-Miguel et al., 2015). Likewise, postmortem examination of the brains of individuals with depression found lower levels of DHA than in controls in brain regions such as the orbitofrontal cortex and cingulate cortex (Conklin et al., 2010; McNamara et al., 2007a). DHA levels were also lower in the prefrontal cortex (PFC) of individuals dying from suicide (McNamara et al., 2013). In addition, the expression of genes involved in PUFA biosynthesis, such as FADS1, were lower in individuals dying from suicide or in patients with depression (Lalovic et al., 2010; McNamara and Liu, 2011). DNA methylation in regulatory regions of the elongation of very long-chain fatty acids protein 5 (ELOVL5) was also associated with major depression and suicide attempts (Haghighi et al., 2015). Other studies, however found no relationship between DHA levels in erythrocytes (Parker et al., 2015; Persons et al., 2014) or in the PFC, entorhinal cortex, and the amygdala (Lalovic et al., 2007; McNamara et al. 2009; Hamazaki et al., 2012; Hamazaki et al., 2013; Hamazaki et al., 2015) with depression or suicide.



Alterations in PUFA status have also been found in bipolar disorder. Most notably, a postmortem study of brains from individuals with bipolar disorder found decreased concentrations of DHA (-24%) and AA (-14%) in the orbitofrontal cortex compared to controls (McNamara et al., 2008), though not in the prefrontal cortex (Hamazaki et al., 2015). Studies of serum, plasma, or erythrocytes from individuals with bipolar disorder indicate decreased concentrations of DHA, as well as altered ratios of fatty acids suggestive of dysregulated PUFA metabolism (Evans et al., 2014; McNamara et al., 2015). Another study in erythrocytes found decreased levels of both DHA and AA in bipolar patients (Chiu et al., 2003). Within a group of bipolar patients, lower serum AA levels were associated with prior suicide attempts (Evans et al., 2012). However, erythrocyte DHA levels in bipolar patients were not correlated with mania severity (McNamara et al., 2015), nor did they change as symptoms improved after treatment with lithium or quetiapine (McNamara et al., 2016).

A number of clinical trials have examined the effects of various n-3 PUFA preparations in depressed patients. Although these studies have had varying results, most meta-analyses and other systematic evaluations of this literature support the efficacy of n-3 PUFAs, particularly EPA or combinations of EPA and DHA, for depression (Appleton et al., 2010; Bloch and Hannestad, 2012; Grosso et al., 2014; Lin and Su, 2007; Martins, 2009; Meyer et al., 2013; Rocha Araujo et al., 2010; Ross et al., 2007; Sublette et al., 2011; Yang et al., 2015). Furthermore, recent studies suggest that certain sub-populations of depressed patients may be more likely to have a beneficial effect from n-3 PUFAs. For example, subjects with higher levels of inflammation showed more improvement in depression when treated with EPA (Rapaport et al., 2015). In another study, depressed patients with low DHA levels were less likely to respond to treatment with an antidepressant drug (Mocking et al., 2015).

Although fewer studies have been done, clinical trials of n-3 PUFAs in bipolar disorder suggest that treatments are well tolerated and may have some efficacy. Controlled, double-blind trials, as well as several open label studies, in adult and pediatric patients indicate beneficial effects of n-3 PUFA treatments on depressive, and sometimes also manic symptoms (Fristad et al., 2015; Osher et al., 2005; Stoll et al., 1999; Wozniak et al., 2015). Studies in which n-3 PUFAs were administered as an add-on to standard pharmacological treatment also found improved mania and depression scores (Clayton et al., 2009), or decreased irritability in patients with that symptom (Sagduyu et al., 2005). Other studies failed to find an effect of n-3 PUFAs in bipolar disorder (Gracious et al., 2010; Murphy et al., 2012); however, metaanalyses support the finding of improved depression, though not mania, in these patients (Rosenblat et al., 2016; Sarris et al., 2012).

### **3.2. Sphingolipids**

*Preclinical findings:* Sphingolipids are, together with cholesterol and glycerophospholipids, the most abundant lipids in brain membranes (Jackson et al., 2005; 2007; Jain et al., 2014) where they form physical barriers. But sphingolipids and cholesterol also play an important role organizing the neurotransmitter signalling and protein-receptor mediated signal transduction. Together, they shape the properties of lipid rafts, which are membrane compartments enriched in G-protein-coupled receptors (GPCR; Hering et al., 2003). Lipid rafts are defined as lateral assemblies within the cell membrane containing high levels of sphingolipids and cholesterol in tight hydrophobic interactions with low levels of glycerophosphocholine (PC; Veiga et al., 2000, 2001). A privileged binding partner of sphingolipids is cholesterol which interacts through its alpha face with other lipids, like sphingomyelins, and through its beta face with transmembrane proteins, like

neurotransmitter receptors. When the composition of lipid rafts changes, e.g., by decreasing levels of either cholesterol or sphingomyelin, this may directly affect receptor affinity, their signalling properties, and subsequent internalization (Fantini et al., 2009; Pike, 2009; Ramstedt and Slotte, 2006; Colon-Saez and Yakel, 2011). Lipid rafts are considered to be the predominant sites where ASM is activated. This activation was shown to enhance ceramide generation in response to various stressors. Ceramide which is highly hydrophobic is concentrated in patches on the cell surface. These patches may rapidly merge to larger platforms or macrodomains and anchor a multitude of membrane-proteins, such as protein kinase C or c-Raf-1, to a specific site. This allocation may enhance oligomerization of specific cell surface proteins including GPCRs (Kolesnick et al., 2000; Cremesti et al., 2002).

Depression-like behaviour can be induced in rodents by the tryptophan hydroxylase inhibitor *p*-chlorophenylalanine (pCPA). A lipidomic analysis revealed that pCPA treatment led to a dysregulation of several lipid species, including sphingolipids, in mice. Sphingomyelin, GalCer, glucosylceramide (GluCer), and lactosylceramide (LacCer) were downregulated, whereas PC and phosphatidylinositol (PI) were upregulated in pCPA treated animals (Weng et al., 2015). A recent study in rats demonstrated that unpredictable stress for several weeks can lead to an increase in ceramide levels in the PFC and hippocampus. Sphingomyelin levels, in contrast, were decreased. In this study, serum corticosterone levels appeared to be negatively correlated with PFC sphingomyelin levels (Oliveira et al., 2015). Interestingly, no significant effects were observed in the amygdala or cerebellum (Oliveira et al., 2015; Miranda and Oliveira, 2015). Chronic stress can induce depression if adequate coping does not develop. However, when coping develops, an aversive emotional reaction emerges, as well as learning of how to adapt to the stress. An example of this type of situation is when a well-established rewarded behaviour is no longer

rewarded (Scully et al., 2000). This usually leads to an extinction of the behaviour, which is an active re-learning of the reinforcement contingency rather than passive forgetting (Quirk and Mueller, 2008; Todd et al., 2014), and is accompanied by an aversive emotional reaction, which may resemble a short depressive state (Papini 2003; Huston et al., 2013). Huston and co-workers have shown that extinction learning is paralleled by a decline in total ceramide, but not sphingomyelin levels in the dorsal hippocampus and cerebellum, but not in the ventral hippocampus of rats (Huston et al., 2016). This effect was probably mediated by a decline in local ASM, but not NSM activity. Interestingly, the degree of re-learning during extinction was associated with the change in ASM activity: the stronger the decline in ASM activity, the more efficiently re-learning occurred (Huston et al., 2016). A reduction in ceramide levels, as it was observed after knocking out carnitine palmitoyltransferase 1C (CPT1C) in mice, was associated with increased filopodia density and reduced spine maturation in hippocampal neurons as well as with impaired learning of a spatial memory task in the Morris water maze (Carrasco et al., 2012). However, in this model, a ceramide-independent role of CPT1C may also contribute to the observed effects. Altogether, these findings suggest a highly dynamic and brain area-specific homeostasis of sphingolipid levels in the brain that is tightly regulated by catabolic and metabolic enzymes. This homeostasis is responsive to normal learning and stress, and potentially involved in rapid behavioural adaptations (Gulbins et al., 2015).

The role of sphingolipids in depression/anxiety was investigated in animal studies using genetically modified mice to manipulate the relevant anabolic and catabolic enzymes. Mice deficient in ASM (ASM KO) typically develop Niemann-Pick disease, a lysosomal storage disorder, in late adulthood. Heterozygous ASM KO did not show the disease phenotype. Nevertheless, the ASM KO mice had reduced ceramide

levels in the hippocampus and reduced anxiety and depression-like behaviours. ASM over-expressing mice (tgASM) showed higher ASM activity and ceramide production in the hippocampus (Gulbins et al., 2013). Increased ceramide levels in the hippocampus resulted in reduced levels of neurogenesis, neuronal maturation, and neuronal survival (Gulbins et al., 2013), which is associated with a depression-like behavioural phenotype (Santarelli et al., 2003; Krishnan and Nestler, 2008; Gulbins et al., 2015). Consistent with these observations, tgASM mice showed a depression/anxiety-like phenotype in several tests including the novelty-suppressed-feeding test, the splash-test, open field, light-dark-box, and forced-swim test (Gulbins et al., 2013; for a review, see: Kornhuber et al., 2014).

Hippocampal neurogenesis is controlled by Akt phosphorylation (Zundel and Garcia, 1998). In tgASM mice, a reduction in Akt phosphorylation at Ser473 was observed (Gulbins et al., 2013). The inhibitory action of C16 ceramide on cell proliferation could be prevented in PC12 cells by a T308DS473Akt1 mutation (Gulbins et al., 2013). Furthermore, corticosterone-stress reduced hippocampal neurogenesis by activation of p38-kinase by an ASM activation-dependent mechanism (Grassme et al., 2015; Jernigan et al., 2015). Ceramide hypo- or hyperfunction, when genetically induced, had no gross effects on synaptic structure or function in the hippocampus (Gulbins et al., 2013). Antidepressant drugs, many of which appear to be functional inhibitors of ASM (Albouz et al., 1986; Kornhuber et al., 2010, 2011), reversed the effects of chronic unpredictable stress on behaviour in wild type and tgASM animals, but not in ASM KO mice. A pharmacological inhibition of ASM with tricyclodecan-9-yl-xanthogenate reduced interferon- $\alpha$  (IFN $\alpha$ )-induced 5-HT uptake in T-cells (Su et al., 2011). These findings suggest that ASM is a functional requirement for antidepressant action in the brain (Gulbins et al., 2013; Kornhuber et al., 2014; Müller et al., 2015).

While ASM exhibits maximal activity in an acidic milieu, there is also a sphingomyelinase that prefers a neutral pH range: the NSM. The pharmacological inhibition of neutral sphingomyelinase 2 (NSM2) with GW4869 reduced the levels of multiple ceramide species in the brain. Inhibition of NSM2 in mice had little effect on episodic memory, but impaired spatial reference memory, and changed N-methyl-D-aspartate (NMDA) and alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor subunit composition and the membrane insertion of these receptors (Wheeler et al., 2009). In contrast, higher ceramide levels, resulting from NSM activity, resulted in increased action potential frequency and reduced slow after-hyperpolarization in hippocampal slice preparations (Norman et al., 2010), effects associated with improved information processing. Pharmacological inhibition of NSM with sphingolactone-24 in T-cells *in vitro* showed a reduced IFN $\alpha$ -induced 5-HT uptake (Su et al., 2011). These findings may suggest that NSM inhibition has an antidepressant effect.

Ceramide in the brain is metabolized by AC. However, depression-like behaviour of rats in the forced-swim test was not affected by pharmacological inhibition of AC with LCL385 (Nahas et al., 2009). In contrast, increased depression-like behaviour was found in AC heterozygous KO mice, which was accompanied by reduced neurogenesis, neuronal maturation, and neuronal survival (Gulbins et al., 2013).

Ceramide is hydrolyzed by ceramidases to Sph. Sph can be re-acylated by ceramide synthases (CerS). Six different CerSs have been described in mammals so far. A spontaneous deficiency in CerS1 activity was identified in lincher mice, which have reduced total brain ceramide and C18- levels, but increased C16 ceramide levels, and exhibit cerebellar and motor dysfunction (Zhao et al., 2011). In contrast, a genetic deletion of CerS1 function decreased C18 ceramide levels in the cerebellum and increased C16- and C22 ceramide levels, but with no net change in total

ceramide level. These effects were associated with attenuated locomotor activity and impaired motor learning, as well as reduced anxiety in the open field test and spatial working memory deficits (Ginkel et al., 2012). In another study, a genetically-induced deficiency in CerS6 led to lower C16 ceramide levels in the thymus, small intestine, and kidney of mice. Only a small decrease in C18 ceramide was observed in the cerebellum of these mice, and no ceramide alterations were detected in the forebrain. CerS6 KO mice were hyperactive in a novel environment, but did not display altered levels of anxiety-related behaviour or changes in novel object recognition (Ebel et al., 2013). These findings suggest that ceramide is not only involved in affective behaviour, but also controls locomotor activity and cognition. Consistent with these findings, repeated injections of C16 ceramide into the dorsal hippocampus of mice produced depression-like behaviour in the novelty-suppressed-feeding and sucrose-preference tests (Gulbins et al., 2013). Likewise, ceramide application in hippocampal slices depressed long-term synaptic responses, an effect mediated by ionotropic glutamate receptors (Vines et al., 2012).

Finally, chronic unpredictable stress, which induces depression-like behaviour, increased hippocampal ceramide levels and reduced neuroneogenesis and neuronal maturation in mice (Gulbins et al., 2013).

Evidence also suggests that the mechanism of action of antidepressant drugs may be mediated, at least in part, through effect of sphingolipids. A lipidomic study suggested that a daily i.p. treatment with the antidepressant drugs maprotiline or paroxetine reduced sphingomyelin species and increased ceramide species, although fluoxetine, maprotiline, or paroxetine had no significant effects on the hippocampal levels of ceramide or sphingomyelin (Lee et al., 2009). These findings suggest that the antidepressant action of a pharmacological treatment may not involve reducing hippocampal ceramide content; however, this study was conducted

in normal mice that had normal basal ceramide levels, thus limiting interpretation of the data to healthy organisms.

In addition to the involvement of sphingolipids in depressive neurochemistry and behaviour, these lipids are also implicated in anxiety. In an early life stress model, mice subjected to stress during early weaning had significant increases in GalCer in the amygdala, though not in the hippocampus or PFC, at 5 weeks of age. GalCer is a major component of the myelin sheath in the brain. The rise in GalCer was paralleled by an increase in anxiety-like behaviour in the elevated-plus-maze test at 5 and 8 weeks of age, suggesting that GalCer in the amygdala may be an important mechanism for the establishment of a hyperanxious phenotype (Ono et al., 2008).

Sphingosine kinases phosphorylate Sph, which is derived from ceramide hydrolysis, to sphingosine-1-phosphate (S1P; Lahiri and Futerman, 2007; Kornhuber et al., 2014). S1P can interact with five different G-protein-coupled receptors: S1P(1)-S1P(5). S1P(2) receptors are exclusively found in hippocampal pyramidal/granular neurons. Mice lacking the S1P(2) receptor (S1P(2)<sup>-/-</sup>) displayed a high rate of spontaneous seizures and cognitive deficits as well as an increase in anxiety-related behaviour (Akahoshi et al., 2011). Restraint stress, which increases anxious behaviour in rats, enhanced serum levels of S1P and sphingosine-1-phosphate. However, it had no effects on Sph or sphingosine levels (Jang et al., 2008, 2011). S1P is known to induce neurogenesis in the brain (Anderson and Maes, 2014), which is required for effective coping with new stressors (Snyder et al., 2011) and for the effects of antidepressant drugs (Santarelli et al., 2003). Thus, an increase in S1P was suggested to play a causal role in stress-induced anxiety and depression. This is supported by findings showing increased anxiety-related behaviour after local infusion of S1P into the cerebral ventricles for 7 days via osmotic mini-pumps. S1P in the brain led to a selective decrease in tyrosine hydroxylase expression in the



amygdala, but not in the cortex. Likewise, expression of extracellular-signal regulated kinase (ERK) and phosphoERK, postsynaptic markers for dopaminergic activity, were not significantly affected (Jang et al., 2011). These findings support the view that stress can cause an increase in S1P levels in specific brain areas, which promotes anxiety-related behaviour.

Another likely mediator of sphingolipid's role in anxiety is sphingosine kinase 2 (SphK2). Mice lacking SphK2 (SphK2<sup>-/-</sup>) express significantly less S1P and dihydro-S1P in the hippocampus. Initial fear responses and the acquisition of contextual fear were not altered in SphK2<sup>-/-</sup> mice; however, they exhibit significantly impaired extinction of fear memory. Thus, while not required for fear-conditioning, S1P appears to be necessary for the extinction of conditioned fear (Hait et al., 2014).

In conclusion, preclinical studies suggest a direct control of depression/anxiety-related behaviour by sphingolipids and their regulatory enzymes in the brain (Müller et al., 2015). Initial findings suggest that this is mediated by their effects on monoaminergic receptor signalling and transmitter synthesis as well as by effects on neuroneogenesis (Gulbins et al., 2015). However, due to their abundance and localization in all neurons, an organisational role for other neurotransmitter systems appears highly likely and awaits further research.

*Human studies:* The quantification of lipids in human brain tissue provides direct evidence for the involvement of sphingolipids in mood disorders. Elevated concentrations of ceramide can be found in the white matter in patients with bipolar disorder (Schwarz et al., 2008). In human brain tissue, Gs $\alpha$  is localized to lipid rafts and other membrane regions. In patients who have died by suicide, Gs $\alpha$  is preferentially bound to lipid rafts in the cerebellum and PFC (Donati et al., 2008), supporting of a role of sphingolipids in depression.

Studies of peripheral tissues also provide indirect evidence for the involvement of sphingolipids in mood disorders. ASM activity was increased in peripheral blood mononuclear cells of patients with major depressive disorder (Kornhuber et al., 2005), plasma ceramide levels were increased in cognitively-impaired patients with depressive symptoms (Gracia-Garcia et al., 2011), and increased ASM activity and ceramide were observed in the blood of patients with post-traumatic stress disorder (Hammad et al., 2012) which is often associated with depression. Plasma ceramide were also found to correlate with depressive symptoms in patients with Parkinson's disease (Mielke et al., 2013). Finally, altered sphingolipid metabolism was found in conjunction with depressive symptoms in a family study (Demirkan et al., 2013). Thus, studies of peripheral samples consistently link increased activity of ASM and/or increased levels of ceramide with a depressive phenotype.

### **3.3. Endocannabinoids**

*Preclinical findings:* The involvement of eCB signalling in the mediation of emotional behaviours is very complex and only partially understood. Administration of cannabinoid agonists in rodents has been reported to induce anxiogenic as well as anxiolytic-like responses, depending on dosage, test paradigm, the test context, test conditions (e.g. light intensity; familiar vs. unfamiliar environment), species or genetic strain. Generally, low doses tend to reduce, and high doses tend to increase, anxiety-like behaviours (for review see: Batista et al., 2014; Moreira and Lutz, 2008; Rubino et al., 2015). Central administration of methanandamide, a metabolically stable analogue of AEA, directly into the PFC induced anxiolytic-like responses in rats for low doses, whereas high doses induced anxiogenic effects (Rubino et al., 2008). Increasing PFC AEA levels by microinjection of URB597 induced anxiolytic responses only at low doses, and had no effect, or even an anxiogenic profile, at

higher doses. In line with this, decreased AEA levels in the PFC, produced by lentivirus-mediated local overexpression of FAAH, produced an anxiogenic response. These findings support an anxiolytic role for physiological increases in AEA in the PFC; however, more marked increases or decreases of this endocannabinoid might lead to an anxiogenic response (Rubino et al., 2008). Less is known about the consequences of heightened 2-AG signalling on emotional behaviour. Recent studies with the MAGL inhibitor, JZL184, report similar anxiolytic-like responses in rodents than for AEA (Blankman and Cravatt, 2013; Rubino et al., 2015). Microinjection studies implicate the amygdala, ventral and dorsal hippocampus, and the dorsal periaqueductal grey as brain regions directly involved in eCB actions on emotional behaviour (Batista et al., 2014).

The eCB system has been suggested to serve as a protective mechanism that is only recruited as needed to restore physiological homeostasis, like for example counteracting the consequences of an aversive or stressful stimulus (Batista et al., 2014; Moreira and Lutz, 2008). Systemic inhibition of endocannabinoid degradation by FAAH/MAGL inhibitors seems to circumvent the biphasic effects by enhancing CB1R signalling in a temporally and spatially restricted manner, thus, reducing anxiety-like behaviours. This might offer an interesting therapeutic potential. Aside from studies investigating acute anxiolytic responses, various studies have reported anti-anxiety and antidepressive effects in studies of the effects of FAAH inhibition, mainly by URB597 and PF-3845, and the MAGL inhibitor, JZL184, in animal models of anxiety and depression, such as chronic unpredictable stress, forced-swim, and restraint stress test, (Batista et al., 2014; Fowler, 2015). However, the preponderance of animal data was obtained in studies using only male rodents. Strong sex differences exist in the prevalence for anxiety and mood disorders, with women being more susceptible to these disorders (Kokras and Dalla, 2014; Fowler, 2015). In

addition, possible undesired central and peripheral effects of chronic eCB degradation inhibition remain to be clarified (Batista et al., 2014; Fowler, 2015). Hence, the translational value of these findings is not completely clear.

*Human studies:* The main features of recreational cannabis use in humans are euphoric and relaxing effects. However, similar to findings in animal studies, cannabis can also induce dysphoric reactions, including severe anxiety, panic, and paranoia. The involvement of eCB signalling in emotional states in humans became most apparent by the unexpected anxiogenic and depressive effects seen in the clinical use of the CB1R antagonist/inverse agonist, rimonabant (SR141716). Rimonabant was initially introduced as a weight-reducing agent, but was withdrawn from the market shortly after its release due to the induction and exacerbation of depressive symptoms and mood alterations. Thus, endogenous activation of the CB1R may serve as a buffer against depression; however, the elimination or reduction of that stimulation can result in depressive symptoms (Van Gaal et al., 2008; Fowler, 2015; Patel and Hillard, 2009).

To date, there are only few direct investigations of the role of eCB signalling in patients with mood and anxiety disorders. Alterations in CB1R expression in postmortem patients with mood disorders predominantly in cortical areas (Hillard and Liu, 2014). Tissue contents of both AEA and 2-AG in the dorsolateral PFC were increased in alcoholic patients who were depressed compared to alcoholics without depression (Vinod et al., 2005). In addition, ventral striatal FAAH activity was higher in alcoholic suicides than in alcoholics (Vinod et al., 2010), which might indicate lower AEA contents in subcortical regions. Altogether, postmortem evidence suggests region-specific alterations in eCB signalling in depressed individuals (Hillard and Liu, 2014).

Peripheral markers of eCB activity are also altered in depression. Notably, serum 2-AG and AEA concentrations were significantly reduced in depressed women compared to controls (Hill et al., 2008, 2009). Moreover, 2-AG concentrations were inversely correlated with the length of the depressive episode (Hill et al., 2008). Based on these findings, it has been suggested that assessment of circulating eCBs may provide a useful biomarker for depression in general, but more importantly, could be used in a personalized medicine approach in which a subgroup of patients with “low eCB” depression might derive more benefit from an eCB-based therapy (Hillard and Liu, 2014).

Although, cannabis is typically the most commonly abused drug in individuals with bipolar disorder, studies addressing a potential pathophysiological involvement of the eCB system in bipolar disorder are rare (Leweke and Koethe, 2008; Ashton and Moore, 2011). Postmortem CB1R expression appears to be unaltered in the anterior cingulate cortex of bipolar patients (Koethe et al. 2007). Similarly, a final conclusion on eCB levels cannot be drawn at present. One study examining eCB levels reported elevation of AEA levels exclusively in schizophrenic patients (Giuffrida et al., 2004), while AEA remained unaltered in patients with dementia or affective disorder; however, the sample size for the affective disorders group was only 22 patients comprised of a mixture of individuals with depressive or bipolar diagnoses. Mixed results have also been reported on the involvement of FAAH polymorphisms, indicating either minor (Monteleone et al., 2010) or no (Pisanu et al., 2013) involvement of FAAH SNPs in bipolar disorder, while neither CNR1 nor NAPE-PLD SNPs were found to be associated with bipolar disorder (Monteleone et al., 2010; Pisanu et al., 2013).

### **3.4. Preventive medicine for mood- and anxiety disorders**

Changes in lipids have been identified in patients with major depressive disorder (Lin et al., 2010). These include lower levels of EPA, DHA and total n-3 PUFAs, consistent with a phospholipid hypothesis of depression (Horrobin and Bennet, 1999). Re-analysis of the prospective randomized PREDIMED study (Estruch et al., 2013) that aimed to prevent cardiovascular events with Mediterranean diet, showed reduced depression scores in diabetic patients (Sanchez-Villegas et al., 2013). A systematic review of cohort studies and a meta-analysis show an inverse relationship between the consumption of n-3 fatty acids and monounsaturated fatty acids with later-occurring depression (Sanhueza et al., 2013, Li et al. 2015). This evidence is limited, as it comes from cohort studies. However, results of a prospective, randomized controlled study point into the same direction: Mediterranean diet with a high content of n-3 fatty acids is associated with lower depression scores in follow-up studies (Sanchez-Villegas et al., 2013). Furthermore, the consumption of n-3 fatty acid can prevent interferon-alpha-induced depression (Su et al., 2014). Long-term prospective interventions studies aiming to prevent depression and anxiety via lipid pathways are currently lacking. Therefore, there are no clear evidence-based recommendations for the prevention of depression via lipid mechanisms.

In humans, a diet rich in PUFAs reduced ceramide levels in serum and muscle tissue (Lankinen et al., 2009). Muscle ceramide has also been found to be reduced after physical exercise (Dube et al., 2011). Conversely, alcohol dependence is associated with increased peripheral lysosomal and secreted ASM activity (Reichel et al., 2010, 2011) and higher concentrations of several ceramide species (Reichel et al., 2015). Oxidative stress plays an important role in the enzymatic and non-enzymatic metabolism of brain lipids (Assies et al., 2014). Oxidative stress induces the ASM/ceramide system and is, in turn, induced by the ASM/ceramide system, leading to a vicious cycle of activation (Kornhuber et al., 2014). Accordingly, the most

definitive current evidence indicates that a Mediterranean diet reduces oxidative stress (Dai et al., 2008), where as alcohol consumption increases oxidative stress (Bleich et al., 2000). In the absence of long-term, high quality prospective studies of lipids in the prevention of mood disorders, and in the absence of evidence based guidelines, a safe recommendation would therefore be a healthy lifestyle with physical exercise, a PUFA-rich diet such as the Mediterranean diet, and the avoidance of excessive alcohol consumption.

#### **4. Lipids in schizophrenia**

##### **4.1. Fatty acids and phospholipids in schizophrenia**

*Preclinical findings:* Depending on the specific manipulation and the point in development when it is made, changes in brain phospholipid fatty acid composition can result in number of neurobiological effects that may be relevant for schizophrenia (Brisch et al., 2014). Most notably, in adult rats with a 70% reduction of brain DHA content resulting from multigenerational treatment with an n-3 PUFA-deficient diet, numerous effects on the dopamine systems were observed, many of which are similar to those associated with schizophrenia (Chalon, 2006). These alterations included decreased densities of dopamine-immunoreactive vesicles, of the vesicular monoamine transporter2 (VMAT2), and the D2 dopamine receptor in frontal cortex suggesting a hypoactivity of the mesocortical projection (Delion et al., 1996; Zimmer et al., 1999, 2000b). In addition, basal dopamine release and the density of D2 dopamine receptors in the Nacc and tyrosine hydroxylase activity in the ventral tegmental area (VTA) were increased suggesting hyperactivity of the mesolimbic system (Zimmer et al., 2000a, 2002). The nigrostriatal system of these rats, on the other hand, appeared normal with respect to dopamine content, D1 and D2 receptor

density, and the density of the dopamine transporter (Delion et al., 1996; Kodas et al., 2002). Another study using a multigenerational treatment model that reduced the concentration of DHA in brain phospholipids by about 80% found differential effects at adolescence and adulthood. Adolescent rats exhibited increased expression of tyrosine hydroxylase in the dorsal striatum, whereas adults had decreased tyrosine hydroxylase protein levels and increased levels of VAMT2 (Bondi et al., 2014). Studies of single generation n-3 PUFA deficiency during pre- and early postnatal development found dopaminergic alterations such as decreased levels of tyrosine hydroxylase and VMAT2 in the hippocampus, and increased D1 and D2 receptor levels in the striatum and cortex (Kuperstein et al., 2005, 2008). However, in adult rats with decreases in brain DHA of only about 20% induced by feeding a diet with reduced n-3 PUFA content from conception, no alterations in the densities of D1 or D2 receptors or the concentrations of dopamine in the Nacc, frontal cortex, or striatum were observed (Levant et al., 2010). This variability in the neurochemical alterations produced by manipulations of brain n-3 PUFA status suggests that the dopaminergic system may be differentially affected depending on the magnitude and timing of the change in brain DHA status, and could potentially interact with effects on maternal behaviour or other factors.

Consistent with the complexity of the effects of PUFA manipulations on dopaminergic neurochemistry, the dopamine-related behavioural changes induced by such treatments also vary between experiments. Several studies found increased locomotor activity in adult rats raised on a n-3 PUFA-deficient diet (Bondi et al., 2014; Levant et al., 2004, 2006c, 2010; Vancassel et al., 2007), although effects varied depending on the age of the rats and the magnitude of the decrease in brain DHA (Levant et al., 2006c, 2010). Likewise, rhesus monkeys with long-term deficiency of n-3 PUFAs exhibited more locomotor activity, as well as stereotyped behaviour, than



those fed a control diet (Reisbick et al., 1994). In another study, however, adult rats with a 70% decrease in brain DHA exhibited less exploratory behaviour in a novel environment (Enslen et al., 1991). Thus, while changes in PUFA status affect the dopaminergic systems involved in motor function, such effects appear to be highly dependent on the specific manipulation.

Manipulation of brain DHA content has also been shown to affect behaviour in animal models of sensorimotor gating (Geyer and Swerdlow, 1997). In a study with rats, which were raised from conception on diets varying in n-3 PUFA content, those with lowest brain DHA levels had significant deficits in prepulse inhibition compared with those with the highest brain concentrations of DHA (Fedorova et al., 2009). In another study the deficits in prepulse inhibition observed in Pax6<sup>+/-</sup> rats, a putative schizophrenia model, were improved after treatment with AA for 4 weeks after birth (Maekawa et al., 2009), suggesting a potential role for n-6 PUFAs in the regulation of sensorimotor gating, at least in this particularly model.

Glutamatergic neurotransmission which is aberrant in schizophrenia (Howes et al., 2015) is also affected by PUFAs. Studies in cultured rat astrocytes and rat brain membrane preparations indicate that free, but not membrane-bound DHA, decreased glutamate uptake (Grintal et al., 2009). In *in vivo* studies, treatment with n-3 PUFAs attenuated the locomotor activity, impaired social interactions, inhibition of startle response, and increased acetylcholinesterase activity induced by the non-competitive NMDA antagonist ketamine (Gama et al., 2012; Zugno et al., 2014, 2015).

Interestingly, at least some antipsychotic drugs may affect n-3 fatty acid homeostasis. Rats treated chronically with risperidone and fed a diet containing ALA had higher erythrocyte and brain DHA concentrations than controls (McNamara et al., 2009b), although sub-chronic haloperidol or clozapine treatment failed to alter brain DHA status in another study of rats fed a standard rat chow (Levant et al., 2006a).

*Human studies:* As with depression, studies suggest that altered brain PUFA composition contributes to the pathogenesis of schizophrenia. Although alterations in a variety of long-chain PUFAs have been observed, meta-analyses support decreased levels of DHA and AA in erythrocyte membranes of schizophrenics compared to controls (Hoen et al., 2013; van der Kemp et al., 2012). Moreover, lower levels of these PUFAs correlated with the severity of symptoms (Bentsen et al., 2012; Montesinos-Rueda et al., 2015; Peet et al., 1996). Similar to the fatty acid differences observed in peripheral tissues, several studies have reported alterations in PUFAs and PUFA-related mediators in certain brain regions postmortem. For example, although some studies found no differences (Hamazaki et al., 2015), lower concentrations of several fatty acids including DHA and AA were found in the orbitofrontal cortex of schizophrenics relative to controls (Hamazaki et al., 2013; McNamara et al., 2007c). Higher levels of calcium-independent phospholipase A<sub>2</sub> and  $\Delta$ 5 desaturase, enzymes involved in cleaving PUFAs from the membrane and PUFA biosynthesis, respectively, were also increased in the brains of schizophrenics (Liu et al., 2009; Rao et al., 2013; Ross et al., 1999). In addition, several PUFA-related genes were associated with schizophrenia, or schizophrenia-related behaviours, including fatty acid binding protein 7 (Fabp7), the phospholipase A2G4A BanI polymorphism, and certain single nucleotide polymorphisms (SNP) of arachidonate 12-lipoxygenase (ALOX12) and Acyl-CoA synthetase medium-chain family member 1 (ASCM1) (Kim et al., 2010; Li et al., 2015; Nadalin et al., 2008; Watanabe et al., 2007).

A relatively small number of clinical trials have tested the effects of PUFA preparations in schizophrenia. Several studies, as well as a meta-analysis, suggest that n-3 PUFA supplements may augment the effects of antipsychotic drugs, but

were not sufficiently efficacious to be used alone (Emsley et al., 2014; Fusar-Poli and Berger, 2012; Jamilian et al., 2014; Joy et al., 2006). Another review of clinical trials, however, was unable to draw firm conclusions regarding the therapeutic utility of n-3 PUFA supplements in this disease (Politi et al., 2013).

#### **4.2. Sphingolipids in schizophrenia**

*Preclinical studies:* GalCer are glycosphingolipids predominantly occurring in oligodendrocytes. They are involved in myelin function. GalCer was shown to be enhanced in the frontal cortex of G72Tg mice, which show a schizophrenia-like phenotype, suggesting that enrichment of GalCer may lead to less compact myelin and ultimately to altered connectivity in the brain (Wood et al., 2014).

Sphingolipids are abundant lipids not only in the brain, but in all tissues. As such it was suggested to use peripheral markers of sphingolipid activity as a proxy marker for brain pathological processes. A study in first-episode treatment-naïve schizophrenics showed significantly reduced total ceramide levels in the skin of these patients. However, while levels of some ceramide subspecies were decreased, others increased (Smesny et al., 2013). Furthermore, the validity of peripheral ceramide levels as an indicator of brain ceramide status remains to be determined. Notably, a study in rats failed to find a quantitative relationship between any single species of ceramide between brain regions and blood (Huston et al., 2016).

Sphingolipids may not only play a role in the pathogenesis of schizophrenia, but also in the therapeutic effects of antipsychotic drug treatment. Mice that received chronic haloperidol treatment for 28 days showed, among other metabolomic changes, a significant decline in brain sphingosine (McClay et al., 2015). Sphingosine is, phosphorylated to S1P, a potent lipid messenger in the brain. A pathway analysis in this study also revealed altered sphingolipid metabolism in the haloperidol-treated

animals. The authors suggested that this may be indicative of altered myelination (McClay et al., 2015). The extent to which sphingolipid changes during antipsychotic treatment are markers for the therapeutic action, or are related to side effects, is currently unclear.

*Human studies:* The first report on sphingolipid metabolism in schizophrenia showed reduced level of galactocerebrosides, total cerebrosides, and sulfatides in a single patient (Cherayil, 1969). Sphingomyelin and galactocerebrosides were reduced in postmortem brain tissue from schizophrenic patients compared to controls (Schmitt et al., 2004). In other post-mortem studies, brains from schizophrenics exhibited significantly lower amounts of PC and phosphatidylethanolamine (PE) (Yao et al., 2000), and ceramide species were more abundant compared to controls, regardless of treatment with antipsychotic drugs (Schwarz et al., 2008). Alterations in phospholipids in brain tissue were found by *in vivo* MR spectroscopy (Fukuzako et al., 1999). A high resolution  $^{31}\text{P}$  NMR spectroscopy study found enhanced sphingomyelin levels in the occipital, but not frontal or temporal cortex grey matter of postmortem schizophrenics (Pearce et al., 2009). A decrease of ceramide (species: 34:1) (Schwarz et al., 2008) and an increase of GM3 and GD3 gangliosides were also observed in untreated schizophrenics (Haselhorst et al., 1988). Total skin ceramides were reduced in schizophrenia with a relative increase in subgroups of ceramide species (Smesny et al., 2012). Altered expression of genes encoding enzymes involved in sphingolipid metabolism were also found in postmortem brain tissue from schizophrenics, independent of antipsychotic medication (Narayan et al., 2009). Genotyping and expression analysis showed an association of N-acylsphingosine amidohydrolase 1 (ASAH1), delta(4)-desaturase, and sphingolipid 2 (DEGS2) genes with the susceptibility for schizophrenia (Zhang et al., 2012; Ohi et

al., 2015), and a network analysis of candidate genes supported the involvement of myelin-related pathways (Rietkerk et al., 2009). GalCer was elevated in the frontal cortex grey and white matter of schizophrenia patients in a postmortem shotgun lipidomic analysis, consistent with findings from mice with a schizophrenia-like phenotype (Wood et al., 2014), suggesting that increased GalCer levels may contribute to the myelin dysfunction and disconnectivity observed in the disease.

Not only were sphingolipid species altered in the brain of schizophrenic patients, but also enzymes that control sphingolipid metabolism. A postmortem mRNA glycogen expression study found 18 genes encoding proteins involved in the sphingolipid pathway differentially expressed in the PFC of schizophrenics with a duration of illness of less than 5 years. In that study, profound decreases in expression were found for 7 genes including serine palmitoyltransferase (SPTLC2), sphingosine-1-phosphate phosphatase (SGPP1), and acid ceramidase 1 (ASA1). Interestingly, in patients with long term illness (>28 years), there was no reduction in expression of genes involved in sphingolipid metabolism; however, one sphingolipid metabolism gene, SPTLC2, was upregulated. These findings suggest a dysregulation of sphingolipid pathways in the brain of schizophrenics during early stages of illness, which may be compensated, or reversed by treatment, at later stages (Narayan et al., 2009). Finally, adult patients with Niemann-Pick disease B and C, often manifest schizophreniform neuropsychiatric abnormalities, further suggest the involvement of sphingolipid metabolism in the etiopathogenesis of schizophrenia (Josephs et al., 2003; Richa et al., 2009; Walterfang et al., 2006). Taken together, abnormalities in the level, metabolism, and genetic regulation of sphingolipids have been found in brain tissue as well as in the periphery, consistent with the membrane hypothesis of schizophrenia (Horrobin et al., 1994). However, the precise roles of single sphingolipids in schizophrenia remain to be determined.

### 4.3. Endocannabinoids in schizophrenia

*Preclinical findings:* Evidence from human and animal research indicates that cannabis use, in particular during critical developmental periods such as puberty and adolescence, acts as a modest statistical risk factor for the emergence of psychosis, ranging from psychotic symptoms such as hallucinations and delusions to clinically significant disorders such as schizophrenia (Caspi et al., 2005; Konings et al., 2008; Arseneault et al., 2004; Schneider, 2008; Rubino et al., 2015; Leweke and Schneider, 2011; Radhakrishnan et al., 2014). Most studies on the role of cannabinoids in schizophrenia have focused on the impact of exogenous cannabinoids on psychosis. However, independent of previous cannabis use, a dysfunctional eCB system has also been implicated in the etiopathogenesis of schizophrenia (Rubino et al., 2015; Marco et al., 2011; Emrich et al., 1997). The eCB system plays an active role in brain regions disturbed in schizophrenia and interacts with the main neurotransmitters thought to be involved in the pathophysiology of schizophrenia. Analysis of eCB levels in animal models of schizophrenia revealed controversial results depending on, among other things, the model and experimental design used and the timing of analysis, i.e. before or after the behavioural testing. One study employing chronic phencyclidine (PCP) administration reported a non-significant reduction in AEA levels in the PFC, whereas 2-AG content was increased in that region (Vigano et al., 2009). In contrast, in a similar pharmacological model, increases in AEA levels in the Nacc and VTA were observed, whereas 2-AG levels were increased only in the VTA (Seillier et al., 2010). More recently, the same group found reduced AEA levels in the PFC and amygdala when PCP-treated rats underwent a social interaction test (Seillier et al., 2013). Isolation rearing in rats, another classical model of aspects of schizophrenia, induced up- as well as down-

regulation of 2-AG contents in a brain region specific manner, while AEA levels remained unaffected (Zamberletti et al., 2012).

Inhibition of FAAH, and subsequent AEA elevation, improved behavioural performance in animal models of schizophrenia (Beltramo et al. 2000; Seillier et al. 2013), supporting the hypothesis for a protective role of AEA in psychosis (Giuffrida et al., 2004). In line with these findings, the non-psychoactive compound, cannabidiol (CBD), which has been shown to exert some of its pharmacological actions via inhibition of FAAH, has been suggested to possess antipsychotic properties in schizophrenic patients and preclinical models for schizophrenia (Leweke et al., 2012; Hermann and Schneider, 2012).

*Human studies:* There is accumulating evidence from clinical research suggesting that AEA dysfunction plays a crucial role in schizophrenia. Alterations in eCB levels in schizophrenic patients were reported in peripheral blood samples (De Marchi et al., 2003), CSF (Leweke et al., 1999; Giuffrida et al., 2004; Leweke et al., 2007), and postmortem brain tissue (Muguruza et al., 2013). The first evidence for eCB alterations in schizophrenia was reported by Leweke et al. (1999), who observed elevated levels of AEA and PEA in the CSF of schizophrenic patients compared to healthy controls. 2-AG was not analysed, as it was not present at a detectable level. This initial finding was replicated in a larger sample of schizophrenic and other psychiatric patients (Giuffrida et al., 2004). Notably, a significant elevation of AEA in CSF of antipsychotic-naïve, first episode schizophrenic patients was found, while serum eCB levels remained unaffected. In addition, CSF AEA levels were significantly decreased and inversely correlated to psychotic symptoms (in particular with negative symptoms) in schizophrenics, with no such alterations detected in patients with dementia or affective disorders. In contrast to these findings, another

study reported higher AEA levels in whole blood of schizophrenic patients compared to controls, and clinical remission was accompanied by a significant drop in AEA contents and the mRNA transcript for FAAH (De Marchi et al., 2003). Consequently, eCB measurements in peripheral blood samples have been criticized, and it is debated whether alterations in peripheral blood reflect changes in the brain and vice versa. Nevertheless, Koethe et al. (2009) reported elevated CSF AEA levels in early psychosis. Interestingly, patients with lower AEA levels showed a higher risk for a transition to psychosis earlier, while higher AEA levels correlated with a delayed transition to psychosis. This anandamidergic up-regulation in the initial prodromal course was, therefore, suggested to indicate a protective role of the eCB system in early schizophrenia. Hence, pharmacological treatment that increases AEA content may possess therapeutic value in schizophrenia, as has been suggested by preclinical studies. Consistent with this hypothesis, CBD produced a decrease in the psychotic symptoms of schizophrenia, which was accompanied by a significant increase in serum AEA levels, and also displayed a markedly superior side-effect profile to the antipsychotic drug amisulpride. Thus, the inhibition of AEA deactivation may contribute to the antipsychotic effects of CBD (Leweke et al., 2012). Although the data implicate a strong involvement of AEA in schizophrenia, the detailed role of eCB signalling in this disorder remains yet to be clarified. A recent study measured eCB levels in postmortem brain tissue from schizophrenic patients and reported elevated levels of 2-AG in the hippocampus, cerebellum, and PFC. AEA levels were decreased in these regions. These postmortem data appear to challenge the assumption that alterations of AEA levels in CSF reflect levels of eCBs in the brain. The discrepancies noted between eCB levels in the brain and whole blood may be the consequence of the modified immune response observed in the course of schizophrenia (De Marchi et al., 2003). Furthermore, substantial changes in eCB



content occur postmortem,, highlighting the importance of the postmortem interval in studies of brain AEA and 2-AG content (Palkovits et al., 2008; Buczynski and Parsons, 2010). Therefore, more studies will be needed to identify the physiological range of eCB concentrations present in various brain regions of schizophrenic patients.

#### **4.4. Preventive medicine in schizophrenia**

Preclinical and clinical research demonstrates that phospholipids, sphingolipids, and eCBs are involved in the ethiopathology of schizophrenia. Supplementation with n-3 fatty acids alters intracellular phospholipase A<sub>2</sub> activity and membrane fatty acid profiles and reduces the risk of progression to first-episode psychotic disorder in young adults with subthreshold psychosis (Amminger et al., 2010, 2015; Smesny, et al., 2014). Studies for the prevention of recurrence of schizophrenic psychoses are currently underway (Pawelczyk et al., 2015). Chronic malnutrition, during which the diet lacks sufficient n-3 PUFAs, as well as other nutrients, appears to enhance the risk of schizophrenia and worsen the symptoms after onset. This is mediated by a reduced DHA content in the brain which affects prominent neurotransmitter systems crucially involved in schizophrenia and antipsychotic action. Much like for depression/anxiety, prevention, or at least limitation, of the schizophrenia risk can be achieved by means of nutrition. Notably, current evidence suggests that a diet high in n-3 PUFAs may have protective effects against schizophrenia, and may also have some minor effects on symptoms once the disease manifests. Thus, n-3 PUFA supplementation may be used to improve therapy outcome.

Accumulating evidence also indicates that sphingolipid homeostasis is disrupted in schizophrenia. Various ceramide species appear to accumulate in the brain, which causes a dysfunction in membrane regulation and signalling. To prevent the

ceramide accumulation, a life style with low stress, no alcohol abuse, and physical activity, all of which reduce ceramide levels, may serve as preventive measure to limit this risk factor for schizophrenia.

Endocannabinoids have long been considered to be a factor that may, when dysregulated, facilitate development of schizophrenia (Berger et al., 2006). Most notably, chronic or acute hyperstimulation of CBRs in the brain, resulting from cannabis use, may lead to schizophrenia-like symptoms. An obvious preventive measure would, therefore, be to abstain completely from any type of drug-induced CBR stimulation, thus avoiding cannabis and other drugs like herbal/legal high preparations (Müller et al., 2015). The potential efficacy of psychopharmacological interventions that reduce eCB activity as a preventive treatment for schizophrenia is currently unclear and awaits further research.

## **5. Lipids in drug addiction**

### **5.1. Fatty acids and phospholipids in drug addiction**

*Preclinical findings:* Little work has been done specifically investigating the role of brain phospholipids in addiction. The studies discussed above indicating alterations in function of the mesolimbic dopamine system, which mediates the reinforcement and reward functions that are fundamentally involved in addiction, in animals raised on n-3 PUFA-deficient diets suggest the potential for brain phospholipids to impact addiction. Studies have also shown that sensitization, a process hypothesized to contribute to the development of addiction (Di Chiara, 1995; Robinson, 1993), to amphetamine is augmented in mice with diet-induced n-3 fatty acid deficiency (McNamara et al., 2008). Likewise, the n-3 PUFA EPA is required for normal

response behaviours and tolerance to alcohol in *C. elegans*, further suggesting a potential role for PUFA in addiction (Raabe et al., 2014).

*Human studies:* The role of phospholipids and PUFA in humans with addiction has yet to be explored.

## **5.2. Sphingolipids in drug addiction**

*Preclinical findings:* The investigation of preclinical models has provided strong evidence that the acute effects of drug use involve changes in sphingolipid metabolism. A widely accepted view is that the over-production of the pro-apoptotic lipid second messenger ceramide could play a central role in the emergence of drug-related disorders. For instance, ceramide upregulation was suggested to be a crucial pathogenic element in a mouse model of emphysema, a prevalent human disease primarily caused by cigarette smoking (Petrache et al., 2005). Likewise, alcohol-induced conditions such as alcoholic liver disease or alcohol-induced neurotoxicity have been associated with the generation of ceramide (Yang et al., 2015). Chronic consumption of alcohol was further shown to alter brain ceramide and sphingomyelin concentrations in rodents in a region-specific manner (Roux et al., 2014). Altered brain ceramide metabolism was also observed in a mouse model of binge drinking (Bae et al., 2014), where ceramide levels decreased during acute intoxication, but increased during withdrawal from alcohol. This biphasic effect might indicate that the consequences of alcohol-induced sphingolipid alterations are not exclusively neurotoxic, but may be also protective and adaptive (Bae et al., 2014).

Few studies have examined the effects of drugs of abuse, other than alcohol and nicotine on sphingolipids. In a murine model of tolerance to opioid-induced antinociception, the repeated administration of morphine resulted in increased activity

of SPT, CerS, and ASM in the spinal cord (Ndengele et al., 2009). In another study, repeated intraperitoneal injection of rats with amphetamine and ethanol resulted in a substance-specific alteration of the concentration of different gangliosides (Haselhorst et al., 1991). Repeated administration of a moderate dose of cocaine in rats led to an accumulation of more complex gangliosides (GM1, GD1a, GD1b, GT1b and GQ1b) and a reduction of precursors (GM3, GM2, GD3 and GD2) in the liver (Cabello et al., 1994). This high sensitivity of sphingolipid metabolism to a broad spectrum of stimuli, suggests that the acute effects of drugs of abuse in general involve sphingolipid-related alterations.

The answer to the question of whether aberrant sphingolipid metabolism can influence drug-related behaviour is less clear. Since sphingolipids are involved in the regulation of ion currents and the secretion, uptake, and signalling of neurotransmitters and hormones including effects on well-known molecular targets in drug addiction (e.g. AMP kinase, BDNF, CREB), there is broad theoretical overlap of sphingolipid metabolism and addiction biology. Moreover, sphingolipids have been shown to be functionally linked to fundamental processes such as neuroplasticity and learning which are relevant for the transition from occasional drug use to addiction (Wheeler et al., 2009). Interestingly, in alcohol-preferring rats a potentially favourable ceramide profile was observed following chronic voluntary ethanol consumption (Godfrey et al., 2015). This might indicate that drug-related behaviour can be utilized to regulate, and possibly even normalize, dysregulated sphingolipid metabolism. Unfortunately, the authors did not mention whether alcohol-preferring rats *per se* exhibited altered sphingolipid levels in comparison to their alcohol-non-preferring counterparts (Godfrey et al., 2015).

Initial studies of the impact of sphingolipids on addiction-related behaviour focused on gangliosides. Gangliosides play a role in synaptic plasticity and may, thus,

contribute to the adaptive changes following drug experience. Long-term administration of GM1 in mice decreased the acute excitatory and behavioural sensitization effects of ethanol (Bellot et al., 1996), as well as amphetamine-induced hyperlocomotion (Bellot et al., 1997). Another group reported that the development of morphine tolerance and dependence was greatly reduced by the co-administration of GM1 by a mechanism involving the translocation of protein kinase C to the plasma membrane (Mayer et al., 1995). In another model, pre-treatment with GM1 enhanced the rewarding properties of cocaine in the conditioned place preference paradigm (Valdomero et al., 2010), which was subsequently shown to involve increased BDNF protein levels in the Nacc (Valdomero et al., 2015). Yet another work suggested that ceramide might be involved in drug adaptation. In a murine model of tolerance to opioid-induced antinociception, the repeated administration of morphine resulted in increased ceramide level. The inhibition of ceramide biosynthesis with various pharmacological inhibitors significantly attenuated the increase in spinal ceramide production and the development of tolerance to morphine's antinociceptive effects (Ndengele et al., 2009).

Consistent with a role for sphingolipids in addiction-related behaviour, modulation of dopamine release or uptake by sphingolipids has also been reported. For example, in the rat pheochromocytoma PC12 cell line, treatment with the  $\text{Ca}^{2+}$ -ionophore A23187 resulted in dopamine release and production of ceramide via the sphingomyelin pathway, both of which were prevented by the inhibition of the A23187-mediated  $\text{Ca}^{2+}$  influx by addition of chelator EGTA (Jeon et al., 2005). Furthermore, treatment of PC12 cells with cell-permeable ceramide increased the rate of dopamine release in the presence of A23187 (Jeon et al., 2005). In another study in PC12 cells, siRNA-mediated or pharmacological inhibition of NSM-2 resulted in decreased ceramide level and decreased dopamine uptake, whereas treatment with cell-permeable

ceramide induced a concentration-dependent increase in dopamine uptake (Kim et al., 2010). Hsp60 was subsequently shown to be a regulator of NSM-2-mediated ceramide production and the concomitant dopamine uptake (Ahn et al., 2013). *In vivo*, the inhibition of the ceramide *de novo* pathway via myriocin treatment resulted in increased dopamine levels in the striatum and hippocampus and reduced dopamine in the cortex, as well as changes in other neurotransmitter systems (Osuchowski et al., 2004). Other studies employing the ceramide synthase inhibitor fumonisins B1 did not find differences in brain dopamine concentrations in BALB/c mice (Tsunoda et al., 1998) or in rats (Porter et al., 1993), but did find effects on the norepinephrine:dopamine ratios in rats, or increased homovanillic acid levels and decreased 5-HT levels in mice. Besides these effects on exo- and endocytic processes, little is known about molecular mechanism involving sphingolipids in addiction-related behaviours.

Sphingosine (Sph), a breakdown product of ceramide, is an endogenous competitive regulator of the sigma 1 receptor (S1R; Ramachandran et al., 2009). The interaction with S1R was specific for Sph, and not observed for ceramide or sphingosine-1-phosphate (Ramachandran et al., 2009). The S1R is found in the CNS and in most peripheral tissues, and is primarily localized in the endoplasmic reticulum. It functions as a molecular chaperone and has been shown to play a regulatory role in many cell signalling systems, including several types of GPCRs and voltage-gated ion channels. Various pharmacological agents including drugs of abuse such as cocaine and methamphetamine bind to S1R, which mediates some of their neuropharmacological effects (Tsai et al., 2014). In fact, activation of S1R was required for establishing the rewarding effect of cocaine in a conditioned place preference paradigm (Romieu et al., 2002). Furthermore, S1R agonists facilitated the reinforcing effects of ethanol and the induction of binge-like drinking (Sabino et al.,

2011), whereas S1R antagonists blocked excessive drinking in alcohol-preferring rats (Sabino et al., 2009). Thus, the regulation of S1R might be a promising link between sphingolipid metabolism and drug addiction. Of note, a single administration of alcohol to pregnant mice induced a more than two-fold increase in the concentration of sphingosine in the brains of progeny (Dasgupta et al., 2007).

*Human studies:* In human studies, ASM activity was increased in blood cells of intoxicated alcohol-dependent patients (Reichel et al., 2010). Further evidence for alcohol-induced activation of the ASM/ceramide system came from the analysis of secretory ASM in blood plasma (Kornhuber et al., 2015), where alcohol-dependent patients exhibited increased ASM activity in comparison to healthy controls (Reichel et al., 2011; Mühle et al., 2014). Alcohol addiction, therefore, is associated with altered circulating blood lipids that might represent potential biomarkers for the disease (Reichel et al., 2015; Meikle et al., 2015). Likewise, increased lung ceramides in individuals with smoking-induced emphysema suggests a crucial role for ceramide upregulation in human drug-related diseases (Petrache et al., 2005). However, whether sphingolipids are involved in the drug-related behaviour of humans or the neuro-adaptation leading to addiction is currently not known.

### **5.3. Endocannabinoids in drug addiction**

*Preclinical findings:* Along with the dopaminergic, the glutamatergic, and the endogenous opioid system, the eCB system has emerged recently as a key neurochemical mediator of reward processes with implications for addictive disorders (Parsons and Hurd, 2015; Friemel et al., 2014; Fattore et al., 2010; Moreira et al., 2015). It has been well known for centuries that cannabinoids can induce euphoric and rewarding effects in humans and animals. The most prominent feature of

consumption of cannabis products is an initial period of euphoria and relaxation. These pleasurable subjective effects most likely contribute to its abuse (Ameri, 1999). Growing evidence implicates the eCB system as a strong modulator of various aspects of drug and non-drug reward (Cota et al., 2006; Fattore et al., 2010; Kirkham, 2009; Panagis et al., 2014; Leishman et al., 2013). Components of the eCB system are widely distributed throughout the brain reward circuits, and eCB signalling exerts a direct or indirect modulatory influence on all other neurotransmitter systems involved in the mediation of reward-related behaviours (Parsons and Hurd, 2015). Furthermore, eCBs are also necessary for the induction of several dopamine-dependent or -independent long-term forms of synaptic plasticity, such as long-term depression and long-term potentiation, in the VTA and in the terminal regions of dopaminergic projections (Kauer and Malenka, 2007). Thus, the eCB system is part of the neurobiological sequelae underlying systematic drug use and the development of addictive behaviours (Müller and Schumann, 2011a, 2011b; Luchicchi and Pistis, 2012; Müller and Homberg, 2015). Given the abuse potential of cannabinoid agonists and the strong impact of the eCB system on basic reward processing, a plethora of preclinical studies has addressed the role of eCB signalling in various aspects of addictive behaviours for all classes of drugs of abuse, as well as natural rewards. A complete overview of the role of eCBs in addiction is beyond the scope of the present review. Accordingly, here we will focus on the rewarding properties of eCBs and their interaction with alcohol, nicotine, opioids and psychostimulants.

AEA and 2-AG are self-administered by nonhuman primates (Luchicchi and Pistis, 2012) and rodents (De Luca et al., 2014) indicating their reinforcing properties. However, the mechanisms by which elevated levels of eCBs produce rewarding effects through FAAH/MAGL inhibition are less clear. Neither FAAH nor MAGL inhibitors induced reinforcing effects or  $\Delta^9$ -tetrahydrocannabinol (THC)-like



psychotropic effects in laboratory rodents. Therefore, they appear to possess little abuse potential. Furthermore, the FAAH inhibitors, URB597 and PMSF, did not alter brain stimulation reward thresholds. Nevertheless, dual FAAH/MAGL inhibition, and to some extent also high doses of the MAGL inhibitor JZL184, exerted cannabimimetic effects. Likewise, chronic FAAH inhibition did not induce any withdrawal symptoms after CB1R blockade in a rimonabant-precipitated withdrawal procedure, while such symptoms were observed after chronic treatment with the MAGL inhibitor JZL184 (Fowler, 2015; Blankman and Cravatt, 2013; Luchicchi and Pistis, 2012). Chronic treatment with the exogenous cannabinoid THC decreased AEA and 2-AG levels in the rat striatum, and levels of AEA but not 2-AG in the midbrain and diencephalon. The CB1R antagonist/inverse agonist rimonabant increased AEA release in the rat hypothalamus, whereas opposite changes were observed for 2-AG release (Panlilio et al., 2013).

Substantial evidence indicates that non-cannabinoid drugs of abuse, such as alcohol, nicotine, opioids, and cocaine, can alter AEA and 2-AG levels in reward-related areas of the rodent brain. However, several factors such as the brain region evaluated, time point of measurement after drug exposure, and the nature of drug exposure (voluntary intake vs. non-voluntary administration) appear to have an important impact on the direction of these alterations (Serrano and Parsons, 2011; Parsons and Hurd, 2015). Repeated nicotine injections increased AEA content in the limbic forebrain, and AEA and 2-AG contents in the brainstem. Hippocampal and cortical levels of both eCB were decreased, whereas, in the striatum, there was a decrease in AEA only (Gonzalez et al., 2002). Intravenous nicotine self-administration increased extracellular levels of both AEA and 2-AG in the rat VTA measured by microdialysis. Interestingly, although VTA 2-AG levels were elevated by both

voluntary and forced (yoked administration) nicotine exposure, VTA AEA levels were increased only by voluntary nicotine self-administration (Buczynski et al., 2013). Surprisingly, given these findings on elevated AEA levels by nicotine and that CB1R antagonism with rimonabant has been suggested as potential therapeutic agent for smoking cessation, there is evidence from a series of experiments in rats and monkeys that FAAH inhibition might counteract the addictive effects of nicotine (Panlilio et al., 2013; Luchicchi and Pistis, 2012). In agreement with these behavioural findings, microdialysis and electrophysiology studies indicate that FAAH inhibition reduces nicotine-induced dopamine elevations in the Nacc shell and blocks nicotine-induced increases in firing rate and burst firing of VTA dopaminergic neurons (Luchicchi and Pistis, 2012). Although the involvement of AEA and CB1R in these effects is not yet completely understood, it is hypothesized that the effects are largely due to activation of peroxisome proliferator-activated receptors (PPAR). The inhibition of FAAH not only raises AEA levels, but also concentrations of other non-cannabinoid *N*-acylethanolamides, i.e., OEA and PEA, which act as endogenous PPAR $\alpha$  ligands (Melis et al., 2008; Luchicchi and Pistis, 2012).

Similar to nicotine, chronic ethanol exposure seems to induce region-specific changes in eCB levels in the rodent brain. Ethanol-induced alterations in eCBs appear to be observed most consistently in striatal regions, but not in frontal cortical areas, although inconsistencies between studies hinder conclusions regarding the direction of change and the brain regions involved (Parsons and Hurd, 2015; Pava and Woodward, 2012). Acute or short-term ethanol exposure decreased eCB signalling, while chronic alcohol exposure appears to be associated with increased formation of AEA and 2-AG contents (Hungund et al., 2002; Pava and Woodward, 2012; Panlilio et al., 2013). As reported previously for nicotine, the nature of drug exposure may play an important role. Forced chronic ethanol intake was reported to

result in a decrease in levels of both AEA and 2-AG in the midbrain, while it increased AEA content in the limbic forebrain (Gonzalez et al., 2002). In contrast, self-administration of alcohol increased 2-AG levels, but did not alter AEA levels in the Nacc shell (Caille et al., 2007). This effect was more pronounced following voluntary self-administration compared with non-contingent alcohol exposure. Hence, brain eCB signalling appears to be influenced not only by drug-related pharmacological effects but, also by motivational aspects of reward processing, such as neural activity engaged by active drug self-administration (Parsons and Hurd, 2015). Pharmacological inhibition or genetic deletion of FAAH increased operant self-administration and preference for ethanol in rats and mice (Parsons and Hurd, 2015; Pava and Woodward, 2012). In addition, an association of impaired FAAH activity with alcohol reward is supported by the findings that an alcohol-preferring phenotype in rats can be established by injecting the FAAH inhibitor, URB597, into the PFC (Hansson et al., 2007).

Functional and cellular cross-talk between the eCB and the endogenous opioid systems is well established. CB1R and  $\mu$ -opioid receptors share a similar distribution throughout the reward circuits and are co-localized, in particular in the Nacc and the dorsal striatum (Parolaro et al., 2010; Lopez-Moreno et al., 2010). In addition, heterodimerization of CB1R receptors with opioid receptors has been reported. Simultaneous activation of CB1R and  $\mu$ -opioid receptors attenuates stimulation of G-proteins or MAPK compared to activation of either receptor alone (Smith et al., 2010; Lopez-Moreno et al., 2010). In the preponderance of preclinical studies, exposure to opioids increased AEA and decreased 2-AG tissue concentrations in the striatum, limbic forebrain and hippocampus (Parsons and Hurd, 2015; Panlilio et al., 2013). FAAH inhibition did not alter the reinforcing efficacy of heroin in an operant procedure; however, increasing AEA levels by AM404, a putative AEA transport

inhibitor, decreased the reinforcing efficacy of heroin. These findings led to the conclusion that modulation of the reinforcing effects of heroin by CB1R activation or inhibition is not due to an opioid-induced release of eCBs, but rather to interactions between opioid receptors and CB1R and their signalling pathways (Solinas and Goldberg, 2005; Panlilio et al., 2013).

Although eCB signalling appears to exert some modulatory impact on the rewarding properties of psychostimulants, this influence appears to be modest, and the detailed role of the eCB system in cocaine reward and addiction remains to be clarified (Oliere et al., 2013; Panlilio et al., 2013). Psychostimulants, such as cocaine, generally produce modest disruptions in brain eCB levels in rodents, with subtle increases in 2-AG in forebrain regions after acute administration and decreases in 2-AG concentration following chronic cocaine exposure. No such changes have been described for AEA. FAAH inhibition does not appear to alter the direct reinforcing effects of cocaine, but might provide protection against cue-induced relapse. Moreover, voluntary cocaine self-administration in the rat did not alter extracellular Nacc eCB levels, but did decrease levels of hippocampal and cortical 2-AG (Panlilio et al., 2013; Parsons and Hurd, 2015).

*Human studies:* Human studies aimed at understanding of the role of eCB signalling in addiction are rare and have primarily focused on alcoholism. Postmortem studies show enhanced AEA and 2-AG levels in the dorsolateral PFC of alcoholic suicide victims, but not alcohol-dependent non-suicides (Vinod et al., 2005). Activity and expression levels of FAAH were decreased in alcoholics compared to controls, but this decrease was lower in alcoholic suicides compared to non-suicides (Vinod et al., 2010). In contrast, a recent study reported decreased MAGL activity in the PFC of alcoholics (suicide and non-suicide victims), while protein levels of FAAH and MAGL

were unaltered (Erdozain et al., 2015). However, it remains quite difficult to draw conclusions on physiological eCB levels in the brain from postmortem analyses, in particular when taking into consideration that the cause of death (suicide vs non-suicide) per se appears to impact on eCB levels.

In healthy social drinkers, visual alcohol cues were found to increase plasma AEA levels, whereas neutral and stress-related images had no such effect. Notably, baseline and response AEA levels in these subjects were negatively and positively correlated with self-reported alcohol craving scores, respectively. Cue-induced increases in heart rate were also correlated with AEA. However, recently detoxified alcoholics had significantly lower baseline plasma AEA levels than non-dependent social drinkers. Although alcohol-related cues elicit more-intense cravings in alcoholics, these individuals did not present significant cue-induced increases in plasma AEA (Mangieri et al., 2009). This blunted AEA response may reflect aberrant eCB processing in alcoholics. Nonetheless, further studies are required to confirm a direct link between this potential peripheral biomarker and brain eCB levels (Parsons and Hurd, 2015).

An increased vulnerability to drug and alcohol abuse in humans has been linked to a polymorphism in the FAAH gene. The SNP rs324420 results in a missense mutation of a C–A replacement at position 385. This leads to a proline to threonine exchange at protein position 129. This C385A SNP is functional and results in reduced FAAH expression and activity, and hence increases plasma concentrations of AEA and other N-acylethanolamine FAAH substrates in individuals with the A/A genotype. This genetic disruption has been strongly implicated in addiction-related behaviours, including enhanced impulsivity and increased anxiety sensitivity, as well as increased risk for drug use (Sipe et al., 2002; Chiang et al., 2004; Buhler et al., 2014; Parsons and Hurd, 2015).

FAAH-based treatments have not yet been approved for human use, but preclinical findings indicate that they might show promise for treating a wide range of disorders, including drug addiction. Early clinical trials with FAAH inhibitors suggest that these drugs are well tolerated, but clarification of their abuse potential requires further evaluation (Panlilio et al., 2013; Fowler, 2015). A clinical trial investigating the safety and efficacy of the FAAH inhibitor PF04457845 for the treatment of cannabis dependence in humans is currently being performed at the Yale School of Medicine (NCT01618656), with results expected in December 2016.

#### **5.4. Preventive medicine for drug addiction**

Drug addiction is a disorder that develops out of controlled drug use and instrumentalization of drug effects, which is often endorsed by society (Müller and Schumann, 2011a, 2011b; Müller, 2013). A second major factor in the etiopathology of drug addiction is the transition from controlled drug use to compulsive use. Currently there is still little evidence for a crucial role of phospholipids and PUFAs in brain neuronal adaptations that lead to compulsive drug taking. However, monoaminergic systems, which undergo major changes during this transition (Müller and Homberg, 2015), are affected by physicochemical properties of the cell membrane, which is at least partially dependent on its phospholipid composition. Thus, a contributory role for PUFAs in addiction development is very likely. Accordingly, investigations to mitigate the transition to compulsive drug use by changing PUFA content in the diet are warranted.

Sphingolipids have been implicated in many organ pathologies caused by chronic consumption of several addictive drugs, many of which result in upregulation of ceramide species in peripheral tissue. However, neurotoxic effects of ceramides have also been observed in the brain. In contrast, little is known about how sphingolipids

contribute to the systematic establishment of drug use behaviours and the loss of control over those behaviours. A recent study suggested that a temporal decline in ceramides may facilitate re-learning (Huston et al., 2016). This suggests that interventions that reduce ceramide load, like the Mediterranean diet or stress reduction, could facilitate the establishment of behaviours that compete with drug-related activities.

A role of the eCB system in drug use and addiction is well established. Most notably, direct stimulation of the CBRs with exogenous ligands, like THC, can lead to an addiction for those substances. However, a growing body of evidence indicates the eCB mediates effects contributing to addiction to other drugs, in addition to THC. Although the eCB can be manipulated by a wide range of pharmacological tools experimentally, no approved effective treatment or preventive measure has emerged yet.

## **6. Conclusion and Outlook**

Accumulating evidence from preclinical and clinical studies suggests an important role for the lipid systems in major psychiatric disorders. Phospholipids and sphingolipids predominantly shape physical properties of cell membranes, while endocannabinoids are involved in cell signalling. Lipids thus represent important loci for synaptic plasticity. Increasing evidence shows that neuronal membranes are not static as previously believed, but are highly dynamic in their lipid composition and, thus, in their microphysical properties. This dynamic regulation of the physical properties of the membrane influences how neurotransmitters interact with membrane-bound signalling proteins, consequently modulating transmembrane information transfer. Findings summarized here highlight emerging models of how

lipid systems act as highly plastic components of neuronal systems that influence their function.

Given this important role for lipids in cell function and plasticity, it is clear that dysfunction in any of the lipid systems may contribute to the etiopathology of psychiatric disorders including mood disorders, schizophrenia, and drug addiction. Furthermore, lipid systems may be altered as a consequence of a primary disorder, such as drug addiction, which can then lead to co-morbidities in peripheral organs.

The data presented here suggest that the use of nutritional and other treatments aimed at modulating the function and regulation of the PUFA/phospholipid, sphingolipid, and eCB systems represent a means to not only improve function and outcomes in individuals suffering from mood disorders, schizophrenia, and drug addiction, but may also serve as means of prevention. Accordingly, these approaches, particularly nutritional treatments, represent readily implementable, inexpensive interventions with emerging mechanistic bases. Furthermore, the reviewed findings support additional investigation of the use of these in interventions as preventative and ameliorative treatments for psychiatric disorders. Future investigation must include controlled randomized trials to determine clinical efficacy, as well as the appropriate formulations, optimal doses, and durations of treatment. Additional studies must fully elucidate the mechanisms by which lipid mediators mitigate the pathophysiology of these psychiatric disorders, and whether the effects differ depending whether the treatment is used for prevention or treatment. The effects of patient characteristics, such as age and gender, on response to lipid interventions also remain to be determined.



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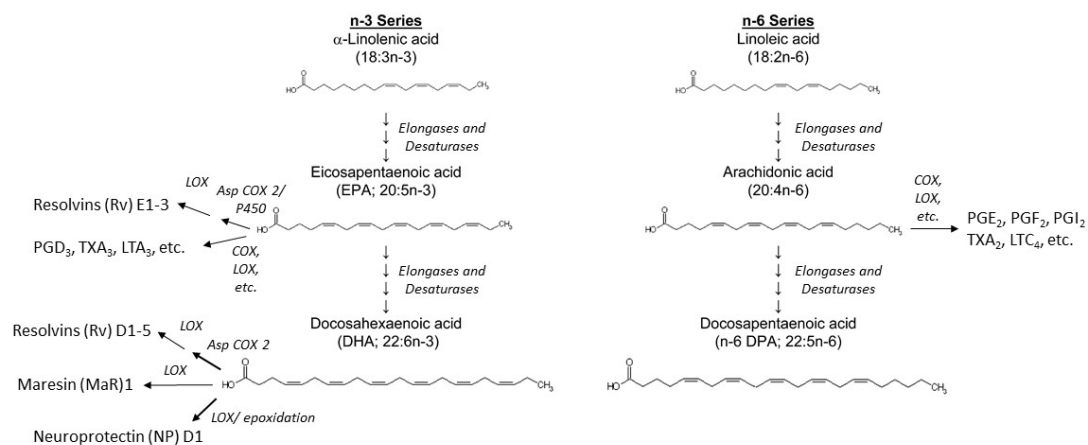
## Figure legends

**Figure 1:** Major synthesis and degradation pathways for polyunsaturated fatty acids (PUFAs).

**Figure 2:** Major sphingolipid synthesis and degradation pathways. Sphingolipid *de novo* synthesis utilizes the condensation of the activated fatty acid palmitoyl-CoA with the amino acid serine. This is catalyzed by serine palmitoyl transferase. The sphingolipid, 3-ketosphinganine (or 3-dehydrosphinganine), which is generated by the *de novo* pathway, is converted to sphinganine, dihydroceramide, and finally ceramide by three consecutive metabolic steps. These steps use the enzymes 3-ketosphinganine reductase, dihydroceramide synthase/ceramide synthase and dihydroceramide desaturase, respectively. The central molecule of the sphingolipid pathway is ceramide. Ceramide also serves for the generation of higher order sphingolipids such as sphingomyelin or glycosphingolipids. These sphingolipids are essential components of the cellular plasma membrane. If ceramide is not used as a structural component, it can either be phosphorylated using ceramide kinase to form ceramide-1-phosphate (not shown), or using ceramidases hydrolyzed to sphingosine. Sphingosine can be phosphorylated to sphingosine-1-phosphate (S1P) by one of two sphingosine kinases. Most of the enzymatic steps in the sphingolipid metabolism are reversible. In a salvage pathway, ceramide is rapidly generated via the breakdown of complex membrane sphingolipids or by recycling of sphingosine or S1P. S1P lyase cleaves S1P into ethanolamine phosphate and hexadecenal, two non-sphingolipid molecules. They define the irreversible exit point of the sphingolipid metabolism (modified from: Lahiri and Futerman, 2007 and Kornhuber et al., 2013).

**Figure 3:** Major synthesis and degradation pathways for endocannabinoids. **A.** At least 3 putative biosynthesis pathways have been suggested for *N*-arachidonylethanolamide (AEA) biosynthesis: 1.) a direct synthesis by hydrolysis of *N*-arachidonoylphosphatidyl-ethanolamines (NArPE) by *N*-acylphosphatidylethanolamine-specific phospholipase D (NAPE-PLD), 2.) a sequential deacylation of NArPE by the  $\alpha\beta$  hydrolase 4 (ABHD4) and the hydrolysis of glycerophosphoethanolamine by the glycerophosphodiesterase GDE1, and 3.) via a phospholipase C (PLC)-like enzyme mediated hydrolysis of NArPEs to phosphoanandamide, followed by dephosphorylation to AEA by a phosphatase, such as tyrosine phosphatase PTPN22. **B.** 2-arachidonoylglycerol (2-AG) is synthesized by hydrolysis of 2-arachidonoyl-containing diacylglycerols (DAG) by either of two enzymes known as sn-1-specific DAGL  $\alpha$  or  $\beta$  (COX2, cyclooxygenase 2; FAAH, fatty acid amide hydrolase; MAGL, monoacylglycerol lipase).

Figure 1



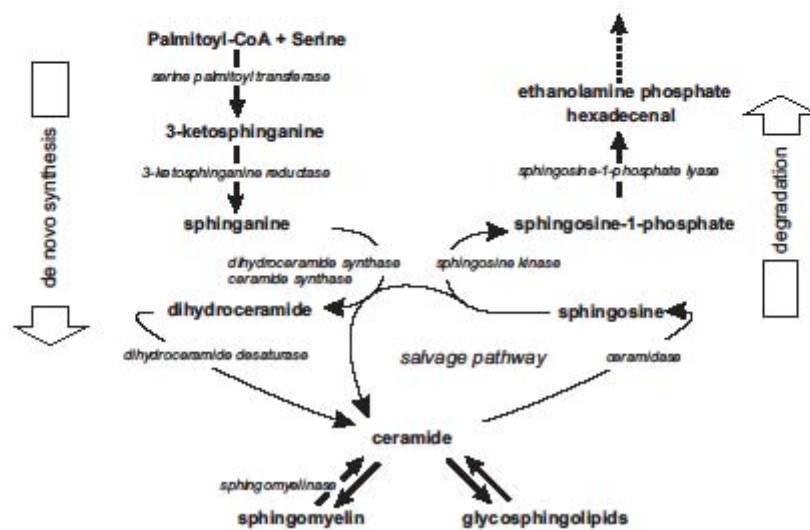


Figure 2

Figure 3

