



# The role of sphingolipids in psychoactive drug use and addiction

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## Abstract

Psychoactive drug use is a common behavior in many societies worldwide, frequently associated with drug instrumentalization. Regular use may develop into drug addiction, which is a severe psychiatric disorder with multiple pathological effects to virtually all organ systems. Treatment strategies for addiction are often insufficient with no broadly working pharmacotreatment available. Recently, lipids, and particularly sphingolipids, have been considered as new mediators in the pathogenic pathways and as possible therapeutic targets for the treatment of addictive states. In our review, we discuss the contribution of sphingolipids in the development of addictive states including alcohol consumption, nicotine, amphetamine, morphine, and cocaine dependencies. Recent data show that the involvement of various classes of sphingolipids, such as sphingomyelins, ceramides, globosides, sulfatides, and cerebroside, might explain the development of some specific features of addictive states, for example, apoptotic neurodegeneration induced by psychoactive substances. On the other hand, protective effects of sphingolipids are discussed. Sphingolipids might be a key mechanism in the development of beneficial effects of moderate alcohol consumption. Therefore, sphingolipid systems emerge as possible new pathways involved in the development of addiction and its pathophysiological consequences. However, further analysis is still needed to investigate the exact mechanisms of sphingolipid contribution and possibility of using of sphingolipids as new therapeutic targets.

**Keywords** Addiction · Lipids · Sphingolipids · Neuroapoptosis · Protective properties

## Abbreviations

alkSM	Alkaline sphingomyelinase	CerS	Ceramide synthases
AMPK	AMP-activated protein kinase	CST	Cerebroside sulfotransferase
ASM	Acid sphingomyelinase	ER	Endoplasmic reticulum
ASM KO	ASM knockout mice	FIASMA	Functional inhibitor of ASM
BDNF	Brain-derived neurotrophic factor	GluCer	Glucosylceramide
C1P	Ceramide-1-phosphate	GSL	Glycosphingolipids
cAMP	Cyclic adenosine monophosphate	IL	Interleukin
Cer	Ceramide	LacCer	Lactosylceramide
CerD	Ceramidase	NADPH	Nicotinamide adenine dinucleotide phosphate
		NMDA	<i>N</i> -methyl-D-aspartate
		NNK	Nicotine-derived nitrosamine ketone
		NSM	Neutral sphingomyelinase
		S1P	Sphingosine-1-phosphate
		Scd-1	Stearoyl-CoA desaturase-1
		SK	Sphingosine kinase
		SL	Sphingolipids
		SM	Sphingomyelin
		SMPD	Sphingomyelin phosphodiesterase
		SMS	Sphingomyelin synthase
		SPL	Sphingosine-1-phosphate lyase
		SPP	Sphingosine-1-phosphate phosphatase
		SPT	Serine palmitoyltransferase

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ST	Sulfatides
tgASM	Transgenic mice with ASM hyperactivity
TNF $\alpha$	Tumor necrosis factor $\alpha$

## Introduction

Lipids are a large family of chemically distinct molecules containing combinations of fatty acids with various backbone structures. Mammalian cells include thousands of lipid species (Wenk 2005; Kimura et al. 2016). A diverse group of hydrophobic or amphipathic lipid molecules possess a variety of functions such as the maintenance of membrane structure, energy storage, signal transduction, regulation of gene expression, and others (Hyötyläinen and Orešič 2014). In accordance with one of the most used classification system LIPID MAPS Lipid, lipids might be classified into eight main groups including fatty acyls, glycerolipids, glycerophospholipids, sphingolipids, sterol lipids, prenol lipids, saccharolipids, and polyketides (Fahy et al. 2005). Lipid metabolism is particularly important for the central nervous system due to the high concentration of lipids in the brain, second only to adipose tissue. Dry human brain contains approximately 60% lipids (Tamiji and Crawford 2010).

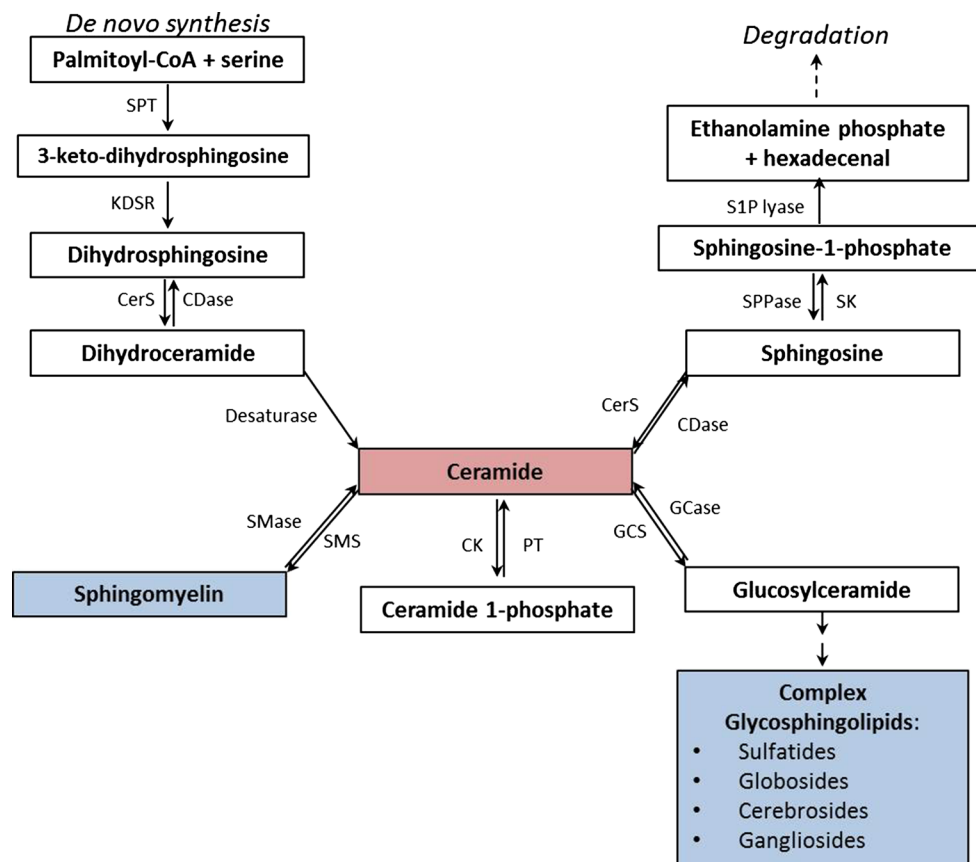
Sphingolipids (SLs), a complex family of compounds with a common long-chain sphingoid base backbone, are particularly abundant in the brain as they constitute 10–20% of the membrane lipids (Holthuis et al. 2001). They comprise ceramides, phosphosphingolipids, glycosphingolipids, and other species, including protein adducts (Fahy et al. 2005). SLs are essential for the development and maintenance of the functional integrity of the nervous system (van Echten-Deckert and Herget 2006; Piccinini et al. 2010; Olsen and Færgeman 2017). Gangliosides are the most abundant group of lipids in the gray matter and in neurons. Sphingomyelin (SM), galactosylceramide (GalCer), and sulfatides are enriched in oligodendrocytes and myelin (Aureli et al. 2015; Olsen and Færgeman 2017). Ceramide serves as the key molecule of the SL metabolism and is involved in the maintenance of vital physiological processes such as cell apoptosis, inflammatory responses and others (Kornhuber et al. 2014).

SL synthesis starts in the endoplasmic reticulum (ER) from the condensation of L-serine and palmitoyl-CoA to 3-ketosphinganine (Fig. 1). This is a rate-limiting reaction catalyzed by serine palmitoyltransferase (SPT) (Merrill et al. 1985; Deevska and Nikolova-Karakashian 2017). Then, 3-ketosphinganine reductase transforms 3-ketosphinganine to sphinganine in a nicotinamide adenine dinucleotide phosphate (NADPH)-dependent manner. Sphinganine is acetylated to dihydroceramide by ceramide synthases (CerS). CerS differ in their specificity to fatty acids of particular acyl chain length and saturation and tissue distribution.

CerS1 and CerS4 mainly produce C18-dihydroceramide and are expressed in the brain, skin, muscles, heart, and liver. CerS5 and CerS6 synthesize C16-dihydroceramide and are expressed in the brain, adipose tissue, intestine, and kidneys. CerS2 is expressed in practically all organs and generates long-chain dihydroceramide such as C20–C26. Similarly, CerS3 produces ceramide (Cer) 24–Cer26. After acetylation, a 4,5-trans-double bond is generated in the sphingoid base to form ceramide (Fei et al. 2011; Brodowicz et al. 2017). This pathway of ceramide biosynthesis is known as de novo pathway. Ceramide is then transferred from the ER to the Golgi apparatus by either vesicular transport or the ceramide transfer protein, CERT1, to reach glucosylceramide synthase or sphingomyelin synthase (SMS) (van Meer and Sprong 2004; Deevska and Nikolova-Karakashian 2017). Then, it is converted to complex sphingolipids through the addition of a phosphocholine group (for SM), glucose (for glucosylceramide), or a phosphate group (for ceramide-1-phosphate). SMS produces SM by transferring the phosphocholine group of phosphatidylcholine to ceramide with the production of diacylglycerol (Deevska and Nikolova-Karakashian 2017).

SM turnover is mediated by sphingomyelinases, a family of enzymes removing the phosphocholine group of SM to produce ceramide. Sphingomyelinases are classified depending on their pH optimum and subcellular localization as either neutral sphingomyelinase (NSM), acid sphingomyelinase (ASM), or alkaline sphingomyelinase (alkSM). ASM has a pH optimum of 5 and is located in acidic lysosomes. In mammals, the expression of a single gene, SMPD1, results in two forms of ASM: the Zn<sup>2+</sup>-dependent lysosomal and Zn<sup>2+</sup>-independent secretory ASM (Kornhuber et al. 2015). Several NSM genes have been described: NSM1 (SMPD2), NSM2 (SMPD3), NSM3 (SMPD4), and mitochondrial-associated NSM (SMPD5). NSM-1 is localized in the ER and Golgi apparatus, but its functions are not well understood. NSM-2 catalyzes SM hydrolysis at the cytosolic face of the plasma membrane, in the multi-lamellar bodies in the cytosol, and at the nuclear envelop (Airola and Hannun 2013; Deevska and Nikolova-Karakashian 2017). Mitochondrial-associated NSM has been discovered in 2010, and has comparable domain architecture and biochemical properties as NSM2 (Wu et al. 2010; Airola and Hannun 2013). Human NSM3 was identified in 2006, but the functional role of it still has to be determined (Krut et al. 2006). This pathway of ceramide synthesis is known as sphingomyelinase pathway.

The last known ceramide synthesis pathway refers to SM recycling called the salvage pathway (Kornhuber et al. 2015). Glycosphingolipids are hydrolyzed to ceramide only in the lysosomes by the combined activity of specific acid hydrolases. Ceramide is further degraded to sphingosine by the ceramidases ACER1, ACER2, and ACER3. Ceramidases are expressed in various cellular compartments and have specific pH optima (Coant et al. 2017; Deevska and



**Fig. 1** Sphingolipids are a class of lipids containing a sphingoid base as a backbone, most commonly the unsaturated amino alcohol sphingosine. Sphingolipids can be synthesized de novo by the condensation of palmitate and serine, which is catalyzed by serine palmitoyl transferase (SPT). 3-Ketodihydrosphingosine is then reduced to dihydrosphingosine by 3-ketosphinganine reductase (KDSR) and then to dihydroceramide by ceramidases (CerS). Ceramide, the key molecule of sphingolipid metabolism, is generated from dihydroceramide by the action of dihydroceramide desaturase. Alternatively, ceramide might be generated from sphingosine by ceramide synthases (CerS) in a salvage pathway of synthesis or from ceramide-1-phosphate by phosphatases (PT). Sphingomyelin is transformed to ceramide by sphingomyelinases (SMase). The only exit pathway from the sphin-

golipid pathways is mediated by sphingosine-1-phosphate lyase (S1P lyase), which metabolises sphingosine-1-phosphate to ethanolamine and hexadecenal. Ceramide might serve as a basis for the generation of complex sphingolipids such as sulfatides, globosides, cerebrosides, and gangliosides via glucosylceramide (Hannun and Obeid 2008; Kornhuber et al. 2014). SPT serine palmitoyl transferase, KDSR 3-ketosphinganine reductase, CerS ceramide synthase, CDase ceramidase, SMase sphingomyelinase, SMS sphingomyelin synthase, CK ceramide kinase, PT phosphatase, GCS glucosylceramide synthase, GCase glucosyl ceramidase, SPPase sphingosine phosphate phosphatase, SK sphingosine kinase, S1P lyase sphingosine-1-phosphate lyase

Nikolova-Karakashian 2017). Sphingosine kinases 1 and 2 (SK1 and SK2) catalyze the phosphorylation of sphingosine to sphingosine-1-phosphate (S1P). Consequently, S1P is either dephosphorylated by the sphingosine-1-phosphate phosphatase (SPP) back to sphingosine, or degraded by the sphingosine-1-phosphate lyase (SPL) to alcoholamine phosphate and trans-2-hexadecenal, two products that cannot re-enter the sphingolipid metabolic pathway (Deevska and Nikolova-Karakashian 2017).

Once formed, ceramide can be converted into more complex sphingolipids through different pathways. Ceramide can be glycosylated by glucosylceramide synthase to glucosylceramide (GlcCer), the main cerebroside, in the Golgi apparatus. More than 300 complex glycosphingolipids can be

produced from GlcCer (Messner and Cabot 2010; Deevska and Nikolova-Karakashian 2017). In the ER lumen, ceramide can be glycosylated to GalCer (Deevska et al. 2009), a precursor of sulfatides. Together with GalCer, sulfatides serve as important components of neuronal myelin in the central nervous system. The addition of galactose transforms GlcCer to lactosylceramide (LacCer) by an intermediate product in the synthesis of more complex glycosphingolipids (Nikolova-Karakashian and Rozenova 2010; Deevska and Nikolova-Karakashian 2017). The biosynthesis of gangliosides also takes place in the Golgi apparatus and starts with the transfer of sialic acid residues to LacCer by specific sialyltransferases—the GM3 synthase, the GD3 synthase, and the GT3 synthase (Groux-Degroote et al. 2017). When the

synthesis is complete, SM and glycosphingolipids (GSL) are relocated to the plasma membrane, where they are known to participate in micro-domain formation (Olsen and Færge-man 2017).

Due to the variety of SL species and the complexity of SL families, many classifications of them exist. For example, SLs can be divided into several major classes: the sphingoid bases and their simple derivatives (e.g., sphingoside-1-phosphate), the sphingoid bases with an amide-linked fatty acid (e.g., ceramides), and more complex sphingolipids with head groups that are attached via phosphodiester linkages (e.g., phosphosphingolipids), via glycosidic bonds (e.g., cerebrosides and gangliosides), and other groups (e.g., phosphono- and arseno-sphingolipids) (Fahy et al. 2005). Slightly simpler classification suggests that SL can be subdivided into SMs/ceramides and GSLs including cerebrosides, sulfatides, globosides, and gangliosides (Dong et al. 2017). In our review, we will use this classification.

Structural diversity of SL determines their multiple functions at the cellular level. SLs modulate the chemical and mechanical properties of all membranes, mediate protein trafficking, ion channel functioning, and cell-to-cell communication. They regulate membrane assembly, vesicle synthesis and trafficking, neurotransmitter release, synaptogenesis, rapid nerve impulse conduction, and signal propagation (Adibhatla et al. 2006; Piomelli et al. 2007; Veloso et al. 2011; Miranda and Oliveira 2015). In the plasma membrane, lipids regulate the membrane's function and generate a barrier between the intracellular and extracellular spaces. Membrane SLs also determine the localization and function of proteins within the membrane and regulate functions of synapses. Moreover, SLs may function within the membrane as second messengers (Müller et al. 2015; Schneider et al. 2017). Moreover, the generation of lipid rafts might serve as one of these mechanisms mediating the effects of SLs. Thereby, SLs and cholesterol form distinct domains in the cell membrane (Brown and London 1998). Hydrophilic carbohydrate head groups of sphingolipids mediate an association between these lipids. Hydrophobic Van der Waals interactions associate the saturated side chains. Cholesterol fills the spaces between the glycosphingolipids to form an ordered structure and to stabilize the domain by tight interactions between its sterol ring system and the sphingosine residue, and hydrogen bonding between the hydroxyl group and the hydrophilic head group of SM. This interaction between SLs and cholesterol produces lipid rafts—distinct membrane domains containing or recruiting proteins under the influence of an appropriate stimulus (Simons and Ikonen 1997; Gulbins et al. 2004). The generation of ceramide in the plasma membrane results in the formation of ceramide-enriched micro-domains that exhibit altered membrane fluidity, change membrane shape, and induce trans-bilayer flip-flop transport (Rebillard et al. 2007; Jenkins et al. 2009).

Membrane domains trap membrane-related proteins and enable the oligomerization of G-protein-coupled receptors (Gulbins et al. 2004; Kornhuber et al. 2014). Thus, changes in the composition of the lipid rafts may affect receptor affinity, signaling, and subsequent internalization. Lipid rafts regulate receptor density and contribute to the regulation of signal transmission (Fantini and Barrantes 2009; Müller et al. 2015). For instance, ceramide-rich platforms mediate a variety of signaling cascades in cells, including activation of B cells, bacterial pathogen infection and cytokine release during infections, and also induction of apoptosis (Maceyka and Spiegel 2014). Lipid rafts are the specific sites for ASM activation and subsequent generation of ceramide, which can explain the involvement of these molecules in the regulation of neurotransmitter homeostasis and development of neurological and psychiatric disorders (Kornhuber et al. 2014; Müller et al. 2015; Schneider et al. 2017; Brodowicz et al. 2017; Müller and Kornhuber 2017). As the brain contains huge amounts of lipids, lipid disturbances in the central nervous system are involved in the pathophysiology of different neurological disorders, including depression, bipolar disorder, schizophrenia, Alzheimer, Huntington's, and Parkinson's diseases, amyotrophic lateral sclerosis, cerebral ischemic injury, and substance use disorder (Wenk 2005; Hillard 2005; Adibhatla et al. 2006; Ciarlo et al. 2012; Blasco et al. 2017; Brodowicz et al. 2017).

Drug addiction is a chronically relapsing disorder that has been characterized by compulsion to seek and take the drug, loss of control in limiting intake, and the emergence of a negative emotional state reflecting a motivational withdrawal syndrome when access to the drug is prevented (Koob and Volkow 2010). Numerous epidemiological surveys show the world-wide importance of drug dependence and abuse (Whiteford et al. 2013; Spagnolo and Goldman 2017). For example, in 2014, 240 million people worldwide suffered from alcohol use disorder, 15 million people consume injectable substances, and 1 billion people smoked tobacco products (Gowing et al. 2015; Brodowicz et al. 2017). However, the majority of people regularly consuming psychoactive drugs are not addicts and will never become such (Abel 1980; Waldorf et al. 1991; Heath 2000; O'Malley and Johnston 2002). For example, in the United States, only 14.9% of the current alcohol drinkers are alcohol dependent. In the European Union, this level is even lower—only 7.1% (Anderson and Baumberg 2006). In most cases, psychoactive drugs are consumed for instrumentalization goals such as the facilitation of social connections, the facilitation of sexual and mating behavior, coping with stress and psychiatric disorders, or cognitive enhancement (Müller and Schumann 2011a, b; McCreary et al. 2015; Müller 2017a, b). The main biological mechanism of controlled drug consumption is related to learning and memory processes. Psychoactive drugs drive learning mechanisms as natural reinforcers.

Positive effects of the drugs and altered mood induce positive memories and maintain the regular consumption (White 1996; Robbins et al. 2008; Müller and Schumann 2011a, b; Müller 2013). A small regular consumption of, e.g., alcohol, was associated with better mental as well as physical health compared to complete abstinence (Skogen et al. 2009). At the same time, negative toxic effects of drugs are associated with negative memories, which determine the controlled use of drugs. However, drug instrumentalization works only in a narrow dose and frequency window. Controlled drug use behavior can be a transitory state for the development of addiction (Müller 2013). Thus, negative life events might lead to an over-instrumentalization and an escalation of drug consumption and drug addiction (Müller and Schumann 2011b; Müller 2017b). These states are characterized by compulsive drug consumption when free choice is not possible anymore. The dosage and frequency of drug intake are substantially increasing. This leads to the development of negative consequences of drug consumption due to chronic poisoning by these substances in toxic doses, and might result in lethal outcome (Hassan et al. 2017).

Although drug instrumentalization is a relatively safe state of drug consumption not requiring pharmacological treatment, drug addiction is a severe medical and social problem, which arises due to the limited number of effective treatments. It might be related to the insufficient understanding of the pathogenic pathways of drug addiction and a lack of effective pharmaco-therapies (McCreary et al. 2015). Recently, it has been shown that various types of SL contribute to the pathogenesis of drug dependence and are proposed as a possible new target for preventive treatment of drug abuse (Schneider et al. 2017). Here, we will discuss the involvement of main classes of SL such as ceramides, gangliosides, sulfatides, and cerebroside as the most studied SL in the development of addictive states and their health impact induced by various psychoactive substances.

## Sphingomyelins and addictive disorders

### Alcohol

#### Peripheral ceramides

Human studies show that patients with acute alcohol intoxication are characterized by a significant increase in lysosomal ASM activity in the peripheral blood cells. ASM is an enzyme catalyzing the breakdown of sphingomyelin to ceramide. Thus, an increase in ASM activity might indicate an elevated ceramide production. This increase is followed by a significant decline within 24 h after beginning of withdrawal. However, withdrawal for 7–10 days is accompanied by a secondary increase in ASM activity and an enhancement

of Cer18:0 levels (Reichel et al. 2010, 2011). In contrast, patients display low ASM activity in the peripheral blood cells in the early phase of withdrawal and increasing activity towards the end of the qualified withdrawal (Reichel et al. 2010). Analysis of secretory ASM activity showed a significant increase in blood serum of alcohol-dependent patients, which was reduced during the abstinence period. Moreover, serum ASM activity reaches normal values already after 1 week of withdrawal (Reichel et al. 2011). Another study has confirmed these findings and showed a gradual decrease of ASM activity during abstinence in patients with acute alcohol intoxication upon admission for treatment. Analysis of gender effect has shown that this trend is similar in females and males, although the initial enzyme activities in females were significantly lower (Mühle et al. 2014).

Animal studies are largely in line with the human data. Clugston et al. (2011) observed a significant increase in the levels of total ceramide, sphingosine, and sphinganine in the liver of alcohol-fed mice. Taking into account that sphingosine and sphinganine are the precursors of ceramide, this increase correlates with the increased ceramide level. However, among the genes controlling ceramide metabolism, only the expression of *Kdsr*, a gene associated with sphinganine synthesis, is changed in alcohol-fed mice. On the contrary, the ceramide plasma concentration in alcohol-fed mice did not differ under these conditions from controls. The authors also showed that alcohol exposure was accompanied by a significant decrease in serum levels of sphingosine and sphinganine in wild-type mice, although the phosphorylated forms of these SLs were unchanged (Clugston et al. 2011). Similarly, a significant decrease in the amount of SMs is found in the blood serum of rats fed with liquid alcohol-containing diet for 8 weeks as well as in alcohol-dependent patients with or without liver disease (Marmillot et al. 2007).

It has been shown that alcohol treatment of rodents re-establishes the composition of SL with various chain lengths and their saturation in the tissue. The levels of SM16:0, SM18:1, and SM18:0 were decreased in the serum, but increased in the heart of mice fed with the Lieber–DeCarli liquid alcohol diet for 4 weeks. Concentrations of Cer18:0 and Cer16:0 were reduced in the liver of these rodents. In the kidneys, the amounts of these ceramides as well as those of Cer18:1, Cer20:0, and Cer22:0 were enhanced after alcohol treatment. Levels of Cer24:1 and Cer24:0 were reduced in the kidneys (Zhao et al. 2011). Another study revealed higher levels of Cer14:0 and Cer18:0 and relatively lower levels of Cer16:0 and Cer20:0 in the livers of chronic alcohol-fed rats. Increased levels of Cer16:0 ceramide could promote cell death (Osawa et al. 2005; Seumois et al. 2007), while Cer18:0 ceramide may inhibit cell growth (Koybasi et al. 2004; Yang et al. 2016). Carr et al. (2014) found an increase in Cer22:0 and Cer24:0 levels in the liver of mice fed with alcohol

for 6 weeks, but no changes in concentrations of Cer16:0, Cer16:1, or Cer24:1 species. The authors reported that the onset of hepatic steatosis and insulin resistance in experimental alcoholic liver disease correlates with an increase in long-chain hepatic ceramides. Liangpunsakul et al. (2010) observed a significant rise in Cer16:0 and Cer18:0 species and a relatively minor increase in Cer24:0 in the liver of alcohol-fed animals (6 weeks protocol), while the concentration of these ceramides was decreased in alcohol-fed ASM knockout (KO) mice.

Altogether, these data indicate that a significant shift in ceramide pattern occurs in peripheral tissues during ethanol treatment. It should be emphasized that several studies reveal a correlation between ceramide accumulation and negative consequences of alcohol consumption. However, as the changes in SL concentrations are multidirectional and differ in various tissues, further investigations are needed to systematize the observed alterations.

Several investigations are devoted to the genetic mechanisms mediating the described changes in ceramide profile induced by toxic effects of alcohol. Longato et al. (2012) have shown that chronic alcohol-related liver disease in humans is associated with an increased expression of multiple genes and proteins promoting ceramide production. These patients are characterized by a significantly increased expression of CerS1, CerS5, CerS6, and SPT1, reflecting an increased ceramide biosynthesis. An mRNA expression of sphingomyelin phosphodiesterase 1 (SMPD1) and SMPD3 genes, which code for ASM and NSM, indicates a high level of SM hydrolysis. A decreased expression of ceramidase 2 (CerD2), an enzyme responsible for deacetylation of ceramide to sphingosine and fatty acids, is also registered during this disorder. Chronic alcohol-related liver disease is also accompanied by significantly higher activities of GM3 synthase and UDP glucose ceramide glycosyltransferase, which mediate the formation of complex SLs from ceramides. Activities of ASM, NSM, and alkSM were also enhanced in the liver of patients with chronic alcohol-related liver disease. These alterations in enzyme activity were associated with higher hepatic levels of the Cer14:0, Cer16:0, Cer18:0, and Cer20:0 species, but not Cer24:0 (Longato et al. 2012). The authors speculate that the cell death associated with chronic alcohol-related liver disease in humans could be mediated in part by increased levels of Cer16:0, as it was shown to promote cell death (Osawa et al. 2005; Seumois et al. 2007), while Cer18:0 inhibits cell growth (Koybasi et al. 2004). Similar results have been found by Ramirez et al. (2013), showing that rats chronically fed with alcohol develop steatohepatitis associated with increased hepatic mRNA expression of CerS4, CerD3, SMPD1, and long-chain subunit 2 of SPT, and significantly reduced expression of SMPD3 and GM3 synthase. Chronic alcohol feeding significantly increases levels of Cer14:0 and

Cer18, and reduces the levels of Cer16:0 in the liver of rats receiving alcohol.

It is not clear yet which exact pathway of ceramide biosynthesis is responsible for alcohol-induced ceramide accumulation. A study of Tong et al. (2014) showed that an inhibitor of de novo ceramide synthesis, myriocin, reduces the concentrations of ceramide in the liver of rats treated with alcohol for 8 weeks and the severity of alcohol-related steatohepatitis including the abundance and sizes of lipid droplets and mitochondria, inflammation, and architectural disruption of the endoplasmic reticulum. These findings suggest that excessive ceramide accumulation is a critical mediator of steatohepatitis in alcohol-related liver disease. Myriocin-mediated reductions in hepatic lipid and ceramide levels are associated with constitutive enhancement of insulin signaling through the insulin receptor and IRS-2, reduced hepatic oxidative stress and modulation of endoplasmic reticulum stress signaling mechanisms. However, focal necrosis and apoptosis persists after myriocin treatment suggesting that the de novo pathway of ceramide synthesis may not play the key role in alcohol-induced cell degeneration in the liver (Ramirez et al. 2013; Correnti et al. 2014). It has also been shown that ASM contributes to the ceramide elevation in alcohol-fed animals (Supakul and Liangpunsakul 2011). An increase in hepatic ceramide after 6-weeks alcohol exposure was associated with enhanced ASM but not NSM activity in the liver (Liangpunsakul et al. 2010). Moreover, ASM KO mice are resistant to the steatosis and apoptotic effects of tumor necrosis factor- $\alpha$  (TNF $\alpha$ ) in the liver (Iimuro et al. 1997; Fernandez-Checa et al. 2005). Liangpunsakul et al. (2010, 2012) observed that the functional inhibitor of ASM (FIASMA; Kornhuber et al. 2010), imipramine, significantly reduces the alcohol-induced increase in the levels of total ceramide as well as Cer16:0 and Cer24:0 species. These changes were associated with an improvement of hepatic steatosis. Presented data confirm the hypothesis that the alcohol-induced ceramide increase is mediated by ASM. However, treatment of alcohol-fed animals with imipramine does not completely inhibit the alcohol-mediated increase in liver ceramide levels (Liangpunsakul et al. 2012), suggesting that alcohol contributes to the elevation of ceramide levels via both de novo and sphingomyelinase pathways. Another ASM inhibitor amitriptyline limits the formation of ceramide in the liver of Long-Evans Cinnamon rats, a genetic model for Wilson disease. It reduces the manifestations of hepatic steatosis, fibrosis and nuclear pyknosis, and improved animal survival (Lang et al. 2007). In ASM KO mice, amitriptyline treatment could also decrease alcohol-induced macrosteatosis and the accumulation of triglycerides and free fatty acids, without causing an SM accumulation (Supakul and Liangpunsakul 2011). Another mechanism for the alcohol-induced increase in ceramide level is the induction of stearoyl-CoA desaturase-1 (Scd-1)

(You and Crabb 2004). Ceramide concentration and SPT mRNA expression are diminished in Scd-1 KO mice (You and Crabb 2004; Supakul and Liangpunsakul 2011).

In vitro studies are in line with in vivo investigations of alcohol effects. A recent study showed that alcohol treatment of isolated hepatocytes reduced the levels of SM and sphingosine and increased ceramide content (Viktorov and Yurkiv 2008). Therefore, it is clear that at least SM pathway is involved in alcohol-induced changes in ceramide metabolism in the liver. However, it cannot be excluded that other mechanisms, particularly the de novo pathway and changes in Scd-1 activity, might also contribute to the observed alterations. Further analysis of possible pathways is needed to understand detailed mechanisms of alcohol action.

It is well known that toxic effects of alcohol result in a variety of degenerative processes in the brain, liver, pancreas, and other organs. It was shown that alcohol-related conditions, such as alcoholic liver disease, alcohol-induced neurotoxicity, hepatic steatosis, or fetal alcohol syndrome are associated with an enhanced production of ceramide and activation of enzymes involved in ceramide metabolism (de la Monte et al. 2009; Wang and Bieberich 2010; Liangpunsakul et al. 2010, 2012; Carr et al. 2014; Yang et al. 2016). Hepatic and serum ceramide levels are shown to correlate with the severity of alcohol-induced steatohepatitis in rats (de la Monte et al. 2009). Alcohol-fed animals are characterized by the augmentation of liver apoptosis. This might be related to the changes in hepatic ceramide level, which are associated with a similar pattern of alterations of caspase-3 activity. These degenerative processes are tightly bound to cell apoptosis. The ceramide/sphingosine rheostat was shown to significantly contribute to the initiation and progression of cell apoptosis in a variety of cells (Cuvillier et al. 1996). Ceramide may participate in hepatocyte apoptosis (Hoekstra 1999; Tsugane et al. 1999) via mitochondria-dependent mechanisms including an increase in reactive oxygen species production and cytochrome *c* release (Garcia-Ruiz et al. 1997; Deaciuc et al. 2000). However, the mechanism of alcohol-induced cell apoptosis mediated by ceramide is still insufficiently studied.

It was also suggested that ceramide could inhibit AMP-activated protein kinase (AMPK) and promote local hepatocellular injury via intensification of the ER stress and apoptosis (Anderson and Borlak 2008; Liangpunsakul et al. 2010; Kuznetsov et al. 2011; Yang et al. 2016). ER stress promotes oxidative injury and inflammation, which might contribute to the progression of alcoholic liver disease. Ceramide accelerates oxidative stress and proapoptotic signaling resulting in reactive oxygen species formation, an increase in lipid peroxidation and in cell death. In turn, reactive oxygen species and inflammatory mediators could increase ceramide generation (Lim et al. 2011). It was hypothesized that ASM could induce ER

stress reflected by an up-regulation of ER stress markers in both HepG2 cells and primary hepatocytes. Currently, it is not clear whether NSM contributes to this pathway. Cultivation of HepG2 cells with exogenous ASM or NSM is followed by an increase in ceramide levels and, in case of ASM, but not NSM, a rise in the levels of ER stress markers. Another study has shown that exogenous ASM, but not NSM increases the expression of ER stress markers (Garcia-Ruiz et al. 2000). Furthermore, inhibition of ASM with amitriptyline prevents alcohol-induced ER stress. Interestingly, ASM KO mice are also resistant to alcohol-induced ER stress and alcohol-mediated sensitization of the liver to lipopolysaccharide effects (Fernandez et al. 2013; Yang et al. 2016).

In HepG2 cells, ASM decreases thapsigargin-induced ER  $\text{Ca}^{2+}$  release, indicating lower ER  $\text{Ca}^{2+}$  storage. The authors suggest that alcohol-induced ASM activation and ER stress, at least in part, by disrupting ER  $\text{Ca}^{2+}$  homeostasis (Yang et al. 2016). The ER structure was severely disrupted in alcohol-exposed liver cells, accompanied by increased mRNA levels of ER stress-related genes (Longato et al. 2012; Ramirez et al. 2013). ER stress may play a critical role in alcoholic liver disease, as it regulates hepatic steatosis and liver injury (Ji and Kaplowitz 2006; Fernandez et al. 2013; Yang et al. 2016). Thus, the ceramide system significantly contributes to alcohol-induced injuries and apoptosis (Yang et al. 2016).

There may be a functional relationship between ASM and cathepsins, molecules triggering apoptosis (Chwieralski et al. 2006). Cathepsin D is a lysosomal target of ceramide (Heinrich et al. 1999). The differentiation of primary mouse hematopoietic stem cells (HSCs) into myofibroblast-like cells is associated with selective ASM stimulation and a cathepsin B and D increase. Inhibition of ASM is followed by the disruption of proliferation of mouse and human hepatic stellate cells (Moles et al. 2010; Yang et al. 2016). Thus, cathepsin-induced apoptosis might serve as another pathway of alcohol-induced cell loss mediated by ceramide.

Taken together, ceramides are shown to contribute to the peripheral effects of alcohol. Ceramides might serve as a key mechanism for alcohol-induced apoptosis in cells of the liver, pancreas, and other peripheral organs. Recent investigations have unraveled a few possible molecular cascades involved in the initiation of alcohol-induced and ceramide-mediated apoptosis. Besides the enhancement of oxidative stress, which is tightly bound to the molecular effects of ceramide (Park et al. 2011), other molecular targets such as cathepsins and  $\text{Ca}^{2+}$  have been observed. However, further investigations are required to understand the mechanisms of ceramide-mediated apoptotic effects of alcohol.

## Ceramides in the central nervous system

A study of Roux et al. (2016) compared alcohol effects on SL levels in the whole brain of juvenile and adult rodents. It was found that ceramide levels, especially Cer16:0, were significantly increased after long-term alcohol drinking in adult animals, but were either decreased or unchanged in the juvenile animals. Alcohol consumption decreases Cer18:0 level in adults, but increases it in juvenile animals (Roux et al. 2016). Thus, a shift in ceramide level is also typical for the central nervous system of animals exposed to alcohol treatment.

Similar results were observed in newborn mice after acute alcohol administration. Time course studies indicate that the levels of ceramide increase significantly in the cortex, hippocampus, and inferior colliculus of 7-day-old mice between 4 and 8 h after alcohol exposure. A robust apoptotic neurodegeneration was induced by acute administration of alcohol associated with ceramide accumulation. An increase in ceramide concentration was coincident with caspase-3 activation in the forebrain. It should be noticed that an increase in the amount of other lipids occurs at later time points mostly 24 h after alcohol exposure. Thus, ceramide may trigger apoptosis in the developing murine brain after alcohol treatment and be a possible missing point between alcohol consumption and development of neurodegenerative disorders (Jana et al. 2009; Saito et al. 2007, 2010).

Several investigations show that ceramide contributes to the development of apoptosis during fetal alcohol disorder. A single dose of alcohol injected to pregnant C57BL/6J mice at gestational day 15–16 resulted in enhanced ceramide and sphingosine amounts in the brain of the offspring. These SL might be a potential mediator of fetal alcohol-induced neuronal loss (Dasgupta et al. 2007). Dasgupta and Hogan (2001) proposed that alcohol-mediated sphingosine toxicity is one possible mechanism of neuronal apoptosis in the brain of progeny mice (Dasgupta et al. 2007). Sphingosine was shown to be cytotoxic in cultured cells (Hannun and Bell 1989), although recent studies did not detect toxicity of even high sphingosine concentrations in epithelial cells (Grassmé et al. 2017; Martin et al. 2017). Acute alcohol administration to mice on postnatal day 7, equivalent to the late third trimester in humans (Godfrey et al. 2015), elevated levels of ceramide in several brain areas such as the cortex, inferior colliculus, and hippocampus. As in adult mice, in pups, these changes were accompanied by an increase in the level of caspase 3, an enzymatic marker of apoptosis. Since alcohol in these animals directly inhibits SPT, it was suggested that the de novo pathway significantly contributes to the development of alcohol-induced apoptosis, particularly in neurons (Olney et al. 2002; Godfrey et al. 2015). These data are confirmed by in vitro studies. The exposure of rat cerebral granule neurons to alcohol results in a ceramide

accumulation. Myriocin inhibits the alcohol-induced ceramide elevation, thus, confirming that the effects of alcohol on SL content in these cells are mediated by the de novo pathway (Saito et al. 2005). In vitro experiments using SPT inhibitors indicate the involvement of de novo ceramide synthesis in various apoptotic pathways such as retinoic acid-induced apoptosis in PCC7-Mz1 cells, A $\beta$ -induced toxicity in hippocampal neurons, oxidative and excitotoxic insults in motor neurons, and hypoxia-induced apoptosis in SHSY5Y cells (Herget et al. 2000; Cutler et al. 2002, 2004; Kang et al. 2009; Saito et al. 2010). However, the activation of sphingomyelinase—and the salvage pathway of ceramide synthesis cannot be excluded yet, as SPT inhibitors do not suppress alcohol-induced caspase-3 activation completely (Saito et al. 2005).

The CerS inhibitor fumonosin B1 did not affect ceramide levels in astrocytes and also not the alcohol-induced increase in ceramide level. Alcohol-induced apoptosis in astrocytes also did not change after fumonosin B1 treatment. However, palmitate, a biosynthetic ceramide precursor, increased ceramide and ceramide-mediated apoptosis in control and alcohol-treated cells. The FIASMA desipramine attenuated the alcohol-induced enhancement in ceramide concentration and in apoptosis (Pascual et al. 2003). Thus, it might be suggested that both, de novo and sphingomyelinase pathways of ceramide synthesis, are implicated in alcohol-dependent accumulation of ceramide and subsequent apoptosis.

Thus, under physiological conditions, SLs such as ceramide are important physiological modulators of normal neuronal development, differentiation, and apoptosis. However, increased levels of these lipids induced by a variety of intra- and extracellular stimuli are implicated in pathological apoptosis of neurons and oligodendrocytes in neuroinflammatory and neurodegenerative disorders such as Alzheimer's disease, HIV-associated dementia, multiple sclerosis, amyotrophic lateral sclerosis, stroke, and particularly, alcohol-induced central nervous system damage (de la Monte et al. 2009; Saito et al. 2010; Chakraborty et al. 2012; Godfrey et al. 2015). Several studies suggest that the ceramide system is a mediator of alcohol-induced apoptosis. Neurodegeneration, white matter atrophy, and increased levels of oxidative stress in human alcoholics are associated with increased expression of genes promoting ceramide production (de la Monte et al. 2008).

## Protective properties of alcohol are mediated by ceramides

Even though ceramide seems to be tightly involved in the development of alcohol-induced neuronal loss and following neurodegeneration, some studies indicate also protective effects of ceramide after alcohol treatment. Experiments of Bae et al. (2014) showed that acute alcohol-induced reduction in ceramides is consistent with a



neuroprotective phenotype. However, an increase in ceramide and a decrease in sphingomyelin levels during withdrawal are associated with a neurotoxic phenotype. Binge alcohol drinking is accompanied by a decrease in the levels of Cer26:0, Cer16:1, Cer18:1, Cer20:1, and Cer22:1 species in the frontal cortex of rodents. An increase in the expression of SMS1 and SMS2 and ACER suggests that ceramide is probably converted to SM and sphingosine/S1P. As an inhibition of ceramide production and an increase in S1P were shown to be protective in a variety of model systems (Culmsee et al. 2002; Haughey et al. 2004; Yung et al. 2012), these data suggest that a shift in ceramide metabolism toward S1P may protect the central nervous system during alcohol intoxication. However, acute withdrawal after binge drinking is followed by a significant increase in the concentrations of Cer16:0, Cer18:0, and Cer20:0 species, which is mostly driven by an enhanced expression of CerS2 and CerS4 (Bae et al. 2014). Although the authors have not identified the neural cell types affected by alcohol, they suggest that astroglia and neurons of the brain may be particularly vulnerable to the toxic effects of alcohol via ASM and NSM-mediated pathways or the de novo pathway of ceramide synthesis (De Vito et al. 2000; Pascual et al. 2003; Schatter et al. 2005; Bae et al. 2014). It was proposed that alcohol withdrawal might induce inflammatory and stress pathways that promote the catabolic formation of ceramide in astrocytes, while de novo ceramide production may be the preferred metabolic pathway for ceramide production in neurons during withdrawal (Bae et al. 2014).

Wang et al. (2013) have shown that prenatal exposure to alcohol induces compensatory neural proliferation and the formation of newborn neurons. Daily intragastrical administration of 25% alcohol to dams promotes an increase in the neural proliferation and the number of newborn neurons in the dental gyrus of pups. Authors speculate that neural proliferation might be the result of a compensatory mechanism for neuroapoptosis induced by alcohol (Jiang et al. 2007; Wang et al. 2013). These data are confirmed by the discovery that the neural proliferation in SMS2 KO pups was enhanced after prenatal alcohol exposure. Thus, the accumulation of intracellular ceramide following the loss of the SMS2 gene results in subsequent compensatory cell proliferation. Neural proliferation is mainly achieved through its phosphorylated metabolite, ceramide-1-phosphate (C1P). The authors suggested that low expression level of protein kinase C (Huang et al. 1999) can be associated with the slowed-down ceramide/C1P cascade. In contrast, alcohol could induce the expression of protein kinase C $\alpha$ . Thus, alcohol-induced accumulation of ceramide could upregulate neural proliferation. Protein kinase C $\alpha$  phosphorylation is a key step for the activation of the ceramide pathway (Wang et al. 2013).

Similar findings on the involvement of ceramide in the protective properties of moderate voluntary alcohol consumption were observed by Müller et al. (2017). It is well known that moderate alcohol consumption reduces the risk for the development of mental disorders such as anxiety and depression (Peele and Brodsky 2000; Skogen et al. 2009). Moreover, moderate drinking, which can be maintained with a high degree of stability, is associated with better health, more close friendships, and more family support than total abstinence (Peele and Brodsky 2000; Skogen et al. 2009). The authors show that alcohol drinking has paradoxical antidepressant effects in initially depressed rodents with genetically enhanced ASM activity (Müller et al. 2017). Mice in which ASM hyperactivity (tgASM) causes a depressive phenotype (Gulbins et al. 2013; Jernigan et al. 2015), drink significantly more alcohol than the wild-type controls. Alcohol drinking is also more susceptible to withdrawal effects in tgASM animals. Interestingly, free-choice alcohol consumption, which allows for self-titration, selectively reduces depression-like behavior in initially depressed tgASM mice. Forced alcohol exposure, in contrast, enhances depression-like behavior in tgASM and wild-type mice alike. The paradoxical antidepressant effects of free-choice alcohol consumption in tgASM mice might be related to the changes in sphingolipid balance of the brain. In wild-type mice, free-choice alcohol drinking reduces the tissue levels of the most abundant SM species, SM18:0, SM18:1, and SM20:0, in the nucleus accumbens and dorsal hippocampus suggesting an increase in corresponding ceramide species. In tgASM mice which showed attenuated basal levels of these SM species, alcohol drinking had the opposite effect and partially reversed the SM decline, thus, at least partly, re-establishing SM homeostasis in the nucleus accumbens, but not in the dorsal hippocampus. In wild-type animals, alcohol drinking had no effect on ASM activity in the brain. In tgASM mice, ASM activity was reduced by free-choice drinking further supporting a drop in ceramide level in this brain structure. Another possible pathway for the paradox antidepressant properties of alcohol in tgASM mice might be mediated by brain monoamines, which may, however, be down-stream of SL homeostasis. Depression induced by ASM hyperactivity coincided with reduced tissue levels of serotonin and dopamine, but not norepinephrine, in several brain structures including the ventral striatum, dorsal hippocampus, and prefrontal cortex. A permanent decline of monoamine tissue levels is associated with depression, and may also render an organisms more prone to addiction (Krishnan and Nessler 2008; Carey et al. 2008; Carr and Lucki 2010; Müller and Homberg 2015). Serotonin and dopamine deficits were partially reversed by alcohol drinking in depressed tgASM mice. In wild-type mice, alcohol drinking by itself reduced dopamine and serotonin tissue levels. These findings suggest that re-establishing SL homeostasis may down-stream

normalize also the serotonin- and dopamine deficits in the brain. The authors speculate that the nucleus accumbens may appear to be a brain region that is particularly sensitive to an SL-dopamine/serotonin interaction, and thus the alcohol effects on SL allostasis (Müller et al. 2017; Müller and Kornhuber 2017).

Experiments by Godfrey et al. (2015) have also shown that ceramides contribute to the beneficial cardioprotective and neuroprotective effects of moderate alcohol consumption. Selectively bred alcohol-preferring rats exposed chronically to alcohol intermittent access drinking showed significantly reduced level of total ceramide in the forebrain and in the heart. These data indicate that alcohol intake during chronic voluntary exposure may have favorable effects on lipid profiles, which may contribute to the beneficial cardioprotective and neuroprotective effects of moderate alcohol consumption (Standridge et al. 2004; Collins et al. 2009; Godfrey et al. 2015). The reduction in the activity of sphingolipid desaturase, *DeGs2*, catalyzing the conversion of dihydroceramide to ceramide, and *ACER1* might mediate alcohol-induced decrease in ceramide levels. However, the activity and expression rate of other enzymes, such as *CerS* or ceramidases, are not changed under these conditions. Therefore, it is proposed that the beneficial effects of voluntary drinking of moderate amounts of alcohol are possibly mediated by a reduction in ceramide synthesis (Godfrey et al. 2015).

Altogether, several investigations reflect the involvement of SLs in the development of alcohol use disorder and related to neurodegeneration and neuronal loss. SLs mediate the toxic effects of alcohol and may contribute to the mechanisms of alcohol addiction. However, another line of studies indicates the protective effects of ceramides against alcohol-induced pathological changes, mostly in the central nervous system. SLs are suggested to mediate beneficial effects of moderate alcohol consumption and might be involved in the mechanisms determining controlled alcohol consumption. These mechanisms might be based on the contribution of SLs to the development of memory traces associated with alcohol consumption, as it is known that ASM/ceramide system is tightly involved in the mechanisms of learning and particularly behavioral extinction (Huston et al. 2016).

## Nicotine

Nicotine smoking is associated with the development of a variety of pulmonary diseases, which are shown to affect SL systems (Tibboel et al. 2013; Seitz et al. 2015). An accumulation of 168 ceramide and SM species with different chain lengths (28 ceramides, 11 dihydroceramides, 19 phytoceramides, 36 sphingomyelins, and 74 GSLs) was observed in the sputum of smokers with and without chronic obstructive pulmonary disease (Telenga et al. 2014). Similar findings

were reported for the lung of cigarette smoke-exposed animals (Petrache et al. 2005; Zulueta et al. 2017). The association between enhanced ceramide levels and lung endothelial and epithelial cell apoptosis was shown in cigarette-smoking-exposed mice (Bodas et al. 2011; Filosto et al. 2011; Zulueta et al. 2017).

These data are in line with the changes observed in the central nervous system of rodents. The administration of one of the main tobacco-specific nitrosamines, nicotine-derived nitrosamine ketone (NNK), to rats was followed by an increase in PS36:1 phosphatidylserine in the cortex and hypothalamus and PS40:6 phosphatidylserine in medial temporal structures, in the cortex and hypothalamus. The mechanisms of smoking-induced changes in the ceramide system are currently unclear. Ceramide accumulation in patients with chronic obstructive pulmonary disease and in cigarette smoke-exposed mice is associated with increased activity of NSM and ASM, thus, reflecting an enhanced SM hydrolysis and ceramide production (Filosto et al. 2011; Lea et al. 2016). On the other hand, inhibition of ceramide synthesis by myriocin and XM462, acting on two different steps of de novo pathway, significantly reduced the outcome of smoking-induced inflammatory cascades, responsible for the induction of chronic damage in the lungs (Zulueta et al. 2017). Thus, ceramide might act as a major mediator of cigarette-smoking-induced damage the peripheral tissues and central nervous system.

## Cocaine

In vitro studies showed that cocaine treatment of cultured Rat-1 fibroblasts induces an increase in total cell phospholipid content, including phosphatidylcholine, phosphatidylserine, and phosphatidylalcoholamine, but not phosphatidylinositol, lysophosphatidylcholine, and cholesterol. A dose-dependent decrease in lysosomal ASM activity can also be induced by cocaine. Cocaine withdrawal was accompanied by a full restoration of ASM activity within 16 h. The authors suggest that the proteolytic degradation of ASM by cocaine might be associated with structural alteration of the enzyme, unknown signal transduction processes (e.g., phosphorylation events) or modification of the lysosomal membrane permeability, resulting in a more pronounced susceptibility to degradation. It was speculated that cocaine and cocaine-induced lipidosis in lysosomes could induce membrane rupture followed by the activation of apoptosis-inducer caspase-3 (Nassogne et al. 2004). Thus, cocaine-induced neurodegeneration might be explained by membrane damage mediated by ceramide as one of the main compounds of biological membranes (Goñi et al. 2014). These data might unravel interesting new therapeutic approaches for the cocaine-induced neurodegenerative disorders by targeting the SL systems.

## Methamphetamine

Self-administration of D-methamphetamine increases ceramide content in the frontal cortex, dorsal, and ventral striatum and, to a greater extent, in the heart, liver, and skeletal muscles of rats. The main effects were observed in the levels of Cer16:0, Cer18:0, Cer24:0, and Cer24:1. A D-methamphetamine-induced increase in the levels of SM16:0, the obligatory biosynthetic precursor of Cer16:0 through the de novo pathway (Gault et al. 2010), and no changes in the levels of SM16:0 or dihydrosphingomyelin 16:0, which generate ceramide through sphingomyelinase-mediated hydrolysis (Gault et al. 2010), reflect the main contribution of de novo pathway to ceramide accumulation. Consistent with this suggestion, D-methamphetamine self-administration was associated with an increase in the transcription of SPT1 and SPT2, and CerS2, CerS4, and CerS6 (Astarita et al. 2015).

Enhanced D-methamphetamine-induced ceramide production was associated with the enhanced expression of genes involved in cell-cycle control (e.g., p21 and p16) and chronic inflammation (e.g., IL-6 and TNF- $\alpha$ ). The authors suggested that D-methamphetamine promotes the generation of free oxygen radicals via cytochrome P450 and nuclear factor- $\kappa$ B, which induce the expression of enzymes involved in the de novo pathway of ceramide biosynthesis, particularly SPT and CerS. In turn, ceramide may induce apoptosis, thus, possibly contributing to D-methamphetamine-induced neurotoxicity (Ellison 1992; Cherner et al. 2010). In line with this suggestion, L-cycloserine, myriocin, and fumonisins B1, inhibitors of SPT and CerS, can prevent D-methamphetamine-induced ceramide accumulation in primary mouse embryonic fibroblast cultures (Astarita et al. 2015). These findings suggest a contribution of SLs and especially ceramides to the neurotoxic effects of D-methamphetamine. Interestingly, as distinct from all previously described addictive drugs, methamphetamine-induced changes in SL content and associated cell injury are mostly driven by the de novo pathway. Further analysis of this feature is needed focusing in particular on SL effects in the brain and their contribution to addiction-related behaviors (Müller 2017a).

## Morphine

Little is known about the contribution of ceramide to the development of opioid dependence. Studies on morphine-induced hyperalgesia and antinociceptive tolerance show that morphine treatment induces an up-regulation of ceramide in the periaqueductal gray and dorsal horn (Bryant et al. 2009; Ritter et al. 2012). This increase was associated with an enhanced activity of ASM, SPT, and CerS, indicating that both de novo and SM pathways are involved in these effects (Ndengele et al. 2009; Ritter et al. 2012). Moreover, the morphine-induced accumulation of ceramide results in

the development of peroxynitrite-derived nitroxidative stress and neuroimmune activation including the activation of glial cells and increased production of TNF $\alpha$ , IL-1 $\beta$ , and IL-6. Inhibition of ceramide biosynthesis with pharmacological inhibitors (myriocin, D609, and FB1) significantly attenuated the increase in spinal ceramide production, nitroxidative stress, and neuroimmune activation (Ndengele et al. 2009). It was also shown that ceramide contributes to the development of morphine-induced apoptosis, which can be fully blocked by FB1 (Bryant et al. 2009). However, even though ceramide contributes to morphine effects, the increased ceramide generation and enzyme expression in the periaqueductal gray region and dorsal horn tissues is most likely involved in the analgesic action of morphine, which might differ from its role in addiction-related behaviors. Thus, further investigation of ceramide involvement in the development of morphine abuse is needed, as this SL seems to interact with the important pathways of drug dependence such as oxidative stress and activation of immune system. Altogether, accumulating evidence shows that various addictive substances increase ceramide activity in peripheral tissues and the brain. So far, this was mostly related to the aversive side effects and/or neurodegenerative effects of those drugs in the brain. Effects in the brain reward system that could contribute to neuroplasticity associated with controlled drug use and addiction are so far only shown for alcohol and await further characterization for other drugs of abuse.

## Glycosphingolipids and addictive disorders

### Gangliosides

Gangliosides are major the components of the neuronal membranes as they account for 10–12% of the lipid content (Posse de Chaves and Sipione 2010). They are located on the external leaflet of the plasma membrane and contribute to the maintenance of neuronal functions such as neuronal development and myelin stability (Palmano et al. 2015; Posse de Chaves and Sipione 2010). The four major brain gangliosides in the adult mammalian brain are GM1, GD1a, GD1b, and GT1b (Tettamanti 2004; Olsen and Færgeman 2017). It is well known that the ganglioside profile changes remarkably during early development of the nervous system as well as throughout life. These changes are region specific (Olsen and Færgeman 2017). Gangliosides have many biological functions as antigens, mediators of cell adhesion, and modulators of signal transduction (Ledeer and Wu 2002). They also play an important role in the development of apoptosis. Specifically, the involvement of GD3 in CD95/Fas-mediated apoptosis in lymphocytes has been extensively studied (Malorni et al. 2007; Saito et al. 2012). Although the majority of gangliosides are found in

glycosphingolipid-enriched micro-domains (lipid rafts) of the plasma membrane (Hakomori 2003), GD3 accumulates within mitochondria of cells undergoing apoptosis (Rippo et al. 2000). The direct interaction of GD3 with mitochondria induces cytochrome *c* release and caspase-3 activation (García-Ruiz et al. 2002; Saito et al. 2012). Recent investigations reveal the involvement of gangliosides in the mechanisms of drug dependence.

## Alcohol

It is known that alcohol treatment alters levels and profiles of gangliosides in several organ systems including the liver and blood plasma (Klemm and Foster 1986; Ruano et al. 1994; Senn et al. 1990; Hannuksela et al. 2002). Long-term alcohol ingestion for 35–56 days reduced the content of gangliosides in the small intestine of rats. The main changes are typical for GM3, a ganglioside accounting for nearly 70–80% of total intestinal gangliosides (Grewal and Mahmood 2010).

In line with these data, the alcohol-preferring line of mice C57BL/6ByJ is characterized by a significantly lower concentration of another ganglioside GM1 in the serum, blood cells, and liver, but not in the cerebellum compared to a non-preferring BALB/cJ line. Interestingly, both acute alcohol treatment and subchronic oral self-administration of alcohol in an alcohol preference test paradigm reduced serum GM1 level in alcohol-preferring animals. However, acute alcohol treatment did not affect hepatic GM1 levels probably due to a higher turnover rate of serum GM1 compared to the liver plasma membranes (Dumontet et al. 1992). Chronic oral alcohol self-administration also reduced the GM1 content in the liver probably mediated by the inhibition of GM1 synthesis or the augmentation of GM1 degradation (Saito et al. 2004). On the other hand, long-term administration of GM1 for 21 days attenuated behavioral sensitization to alcohol measured as locomotion frequency of mice in the open-field test, but did not affect alcohol blood levels (Bellot et al. 1996). Thus, it can be suggested that peripheral GM1 might play an important role in the regulation of controlled alcohol use. However, further analysis of changes in GM1 level during voluntary drinking is needed to understand the role of central structures in this process.

As distinct from the peripheral tissues, an increase in GM3 levels in the frontal cortex was observed after the subchronic treatment with alcohol for 20 days. However, levels of GM1, GM2, GQ1b, GD1a, or GT1b were not affected by this type of treatment (Haselhorst et al. 1991).

Prenatal treatment with alcohol was accompanied by a decrease in whole brain GM1 levels. GD3 was decreased at postnatal day 5, then increased by day 15, and again decreased at day 21. Level of GM1 increased at postnatal days 15 and 21. A reduction in GM1 concentration indicates abnormal myelinogenesis, as GM1 is considered as a marker

of myelin. GM1 was shown to promote *in vitro* neuritogenesis and *in vivo* re-myelination (Farooqui et al. 1997; Fang et al. 2000; Dasgupta et al. 2007).

*In vitro* studies show that alcohol treatment induces a decrease in ceramide long-chain base moiety in the rat cerebral granular cells, but does not affect the rate of *de novo* biosynthesis of gangliosides labeled in the oligosaccharide moiety. These data indicate that in the presence of alcohol, *de novo* biosynthesis of ganglioside long-chain base moiety strongly decreases, while the biosynthesis of the ganglioside oligosaccharide portion is almost unaffected. An alcohol-induced increase in the levels of radioactive GD1b and GT1b suggests that alcohol increases the sphingosine salvage pathway for ganglioside biosynthesis. The authors suggest that the alcohol-induced increase of sphingosine metabolism constitutes a mechanism of cell defense during alcoholic stress. Moreover, a decrease in ganglioside concentration in the cells induced by alcohol might also have important consequences on cell events such as growth, signal transduction, apoptosis, and proliferation (Ravasi et al. 2002). However, gangliosides do not react uniformly to alcohol administration. Both main pathways of ganglioside synthesis seem to contribute to alcohol-induced changes in ganglioside pattern of the brain and peripheral tissues.

Gangliosides may also contribute to alcohol-induced apoptosis. It was observed that prenatal alcohol treatment induces a wide-spread apoptotic neurodegeneration within 24 h associated with a significant increase in GM2 level in the brain of progeny mice. This increase was most pronounced in the cingulum and the cingulate/retrosplenial cortex. However, the levels of other major gangliosides, such as GD1a, GD1b, and GM1, were unchanged after prenatal alcohol exposure. The elevation of GM2 is observed initially in apoptotic neurons and later in activated microglia. The authors suggest that GM2 is present in both mitochondria and lysosomes/phagolysosomes of neurons and activated microglia in the alcohol-exposed brains, although GM2 expression is stronger in activated microglia than in neurons. Thus, GM2 elevation in mitochondria and GM2-induced cytochrome *c* release from mitochondria reflect the involvement of GM2 in alcohol-induced mitochondrial apoptosis (Saito et al. 2012). It can be suggested that as well as ceramides, an increase in the levels of some gangliosides in the brain after alcohol treatment might mediate the neurodegenerative effects of this substance.

In contrast, another ganglioside, GM1, appears to have protective properties against alcohol-induced adverse effects in the central nervous system. The addition of GM1 to culture media or *in vivo* administration to rodents reduces the teratogenic/toxic effects of alcohol (Hungund and Mahadik 1993; Hungund et al. 1994). GM1 reverses alcohol-induced growth retardation and alteration of morphological properties in cortical cells (Laev et al. 1995). GM1 provided

protection against alcohol neurotoxicity in hippocampal neurons of fetal rats and in dorsal-root ganglion neurons from embryonic chicks (Heaton et al. 1994). Pretreatment with gangliosides and LIGA20, a semisynthetic derivative of GM1 ganglioside, attenuated alcohol-induced apoptosis and the following apoptotic processes, such as cell death, DNA fragmentation, and caspase-3 activation, in cultured rat cerebellar granule neurons. The effects of GD1b and GT1b under these conditions were more pronounced than the effects of GM1 (Saito et al. 1999).

Similar findings were obtained by *in vivo* models. LIGA20 and GM1 partially reduced alcohol-induced widespread neurodegeneration and activation of caspase-3 in the cingulate and retrosplenial cortices of mice. The attenuation of alcohol-induced apoptotic neurodegeneration by these substances might be related to the regulation of growth factors and neurotrophic factors by gangliosides (Hakomori et al. 1998; Ledeen et al. 1998; Saito et al. 2007). It was shown that GM1 activates Trk-type receptors in cultured neurons (Bachis et al. 2002; Duchemin et al. 2002). Alcohol induces impairments in the functions of neurotrophic factors including brain-derived neurotrophic factor (BDNF) via the blockade of NMDA receptors (Spanagel 2009). This leads to a Bax-dependent activation of caspase-3. The activation of Trk receptors by GM1 stimulates survival pathways such as the PI3K/Akt pathway (Yao and Cooper 1995) and the extracellular signal-regulated kinase pathway (Climent et al. 2002). Thereby, GM1 protects against alcohol-induced apoptotic neurodegeneration. Authors speculate that GM1 and LIGA20 also regulate intracellular  $Ca^{2+}$  levels (Ledeen and Wu 2006; Saito et al. 2007), which are known to have a critical role in apoptosis and are disrupted by alcohol through the blockade of NMDA receptors (Saito et al. 2007). This, under certain conditions of alcohol treatment gangliosides might have neuroprotective and anti-apoptotic effects at least partly mediated by growth and neurotrophic factors. These data might provide an input in the hypothesis on SL contribution to positive effects of alcohol instrumentalization described previously.

Altogether, accumulating evidence suggests that gangliosides are involved in the regulation of both, controlled alcohol consumption and toxic effects of alcohol. Opposite effects of various gangliosides, particularly neuroprotective effects and pro-apoptotic properties, might determine the contribution of SLs to those effects. It might be suggested that the transition from controlled alcohol use to alcohol addiction is at least partly mediated by the changes in the synthesis pattern of gangliosides.

### Cocaine

An accumulation of complex gangliosides such as GM1, GD1a, GD1b, GT1b, and GQ1b, and a reduction of

precursors GM3, GM2, GD3, and GD2 in the rat liver were observed after repeated cocaine administration. The authors suggest that the observed changes in ganglioside synthesis are mediated by an alteration of vesicular transport from cis- to trans-Golgi cisternae, induced by either cocaine or its metabolites (Cabello et al. 1994).

Prenatal treatment with cocaine was followed by a significant elevation of whole brain content of neutral glycosphingolipids and total gangliosides in 1-day-old mice (Leskawa et al. 1994). Elevated levels returned to control value already at postnatal day 11 (Leskawa et al. 1994).

Experiments by Valdomero et al. (2010) showed that GM1 pretreatment 2 h before cocaine injection, which did not have any effect by itself, increased the rewarding effect of cocaine in the conditioned place preference test (Huston et al. 2013). This enhancement correlated with a significant increase in the brain's cocaine level. However, pharmacokinetic parameters, such as plasma bound/free cocaine ratio, permeability of the blood-brain barrier for cocaine, and activity of brain and serum acetylcholinesterase and butyrylcholinesterase, were not changed by GM1. It also did not influence the inhibitory effect of cocaine on the dopamine transporter, a major mediator of cocaine addictive properties in the brain. A follow-up study showed that GM1 administration induces a significant increase in BDNF protein levels in the nucleus accumbens, which might explain the increased rewarding effects of cocaine in the conditioned place preference test (Valdomero et al. 2015). Similar findings have been observed by Lim et al. (2011), demonstrating an enhanced release of mature BDNF in hippocampal neurons and both mature BDNF and pro-BDNF in human neuroblastoma cells after GM1 treatment. Moreover, GM-1 also partially reversed the anti-proliferative effect of cocaine in PC12 cells. It was shown that GM1 can act as a neurotrophic factor supporting the development of some midbrain dopaminergic neurons (Tosk et al. 1996). Thus, it can be suggested that an increase in GM1 level observed in the brain after repeated cocaine administration might serve as a mechanism for the development of cocaine addiction as it enhances the rewarding properties of this drug. Interestingly, this effect of GM1 is mediated by BDNF, which is considered as a brain-protective molecule. Further analysis of GM1-induced involvement of BDNF in cocaine dependence is warranted.

### Amphetamine

Subchronic treatment with amphetamine for 20 days resulted in an increase in GQ1b, but not GD1a, GM2, or GM3 concentrations in the brain of rats (Haselhorst et al. 1991). Bellot et al. (1997) showed that repeated administration of the exogenous ganglioside GM1 for 7 days does not affect the locomotor activity behavior of mice, but decreases

amphetamine-induced hyperlocomotion. However, acutely administered GM1 does not affect amphetamine-induced locomotion. The authors proposed that ganglioside treatment may affect synaptic plasticity, thus, modifying the induction of the adaptive changes following drug treatment. The GM1-induced attenuation of the development of behavioral sensitization to the locomotor-stimulant effect of amphetamine might be mediated by the influence of this ganglioside on the dopaminergic system. This view is supported by the observation that GM1 has neuroprotective effects in different lesion models of the dopaminergic nigrostriatal pathway (Jackson et al. 1989; Schneider and DiStefano 1995). Supersensitivity of dopaminergic neurons developed after the treatment combination haloperidol/GM1, measured in the open-field test and by apomorphine-induced stereotypy (Vital et al. 1995). GM1 administered after haloperidol withdrawal enhanced the increases in both, general activity in the open field and apomorphine-induced stereotypies (Bellot et al. 1997). Thus, it can be suggested that GM1 affects synaptic plasticity in the brain of rodents, facilitate the induction of the adaptive changes in receptor function, and, thus, exerts protective effects at various stages in the development of amphetamine dependence.

Interestingly, as practically all types of drug addiction are mediated by dopaminergic system (Volkow et al. 2017), the effects of gangliosides on this neurotransmitter might be critical for understanding of the role of these lipids in the mechanisms of drug dependence. Further detailed analysis of molecular mechanisms of ganglioside effects during dependence states is needed. These data might explain the contribution of gangliosides not only to amphetamine dependence, but also to all other types of drug abuse.

### Morphine

It is now agreed that gangliosides contribute to the development of morphine tolerance and antinociception (Crain and Shen 2000, 2007; Mayer et al. 1995; Angheliescu et al. 2015). Moreover, some authors suggested that these effects might also play an important role in morphine dependence (Crain and Shen 1998). Treatment of dorsal-root ganglion neurons with GM1 in low doses induced an opioid excitatory supersensitivity, manifested by a decrease in the threshold concentration of a  $\kappa$ -opioid peptide dynorphin (1–13) and morphine required to prolong action-potential duration. Other gangliosides, such as GD1a, GD1b, GQ1b, GM2, and GM3, did not have these effects. The efficiency of opioid excitatory receptor functions after GM1 treatment increased in a way that even a weak partial agonist, naloxone, became effective in prolonging action potentials in these neurons. However, antagonist properties of naloxone at opioid receptors were not altered by GM1. The authors suggested that the effects of GM1 are related to the

enhanced binding activity of naloxone to  $G_s$ -coupled opioid receptors. GM1 binds to opioid receptors and induces a conformational change in the receptor–G-protein association, thus resulting in switching of receptor-coupling from normal inhibitory  $G_i$ -coupled signaling mode to an excitatory  $G_s$ -coupled signaling mode. These data indicate that GM1 is required for the development of cellular manifestations of tolerance and physical dependence (Crain and Shen 1998, 2000, 2007). Systemic administration of the CTX-B subunit of cholera toxin, which selectively binds GM1 at the plasma membrane, also enhances morphine's analgesic potency and blocks opioid tolerance (Crain and Shen 2004).

However, it should be noticed that these effects are typical only for GM1 in low doses. High doses of GM1 attenuated the development of morphine tolerance and dependence (Shen and Crain 1990). GM1 in high doses blocked the translocation of protein kinase C from the cytosol to the neuronal surface membranes (Shen and Crain 1990; Crain and Shen 2004).

Thus, GM1 in various concentrations is shown to have different effects on cell response to morphine. Further analysis of thin mechanisms of these differences might not only unravel the pathways of morphine dependence mediated by SLs, but also propose new possible treatment strategies for this disorder.

### Sulfatides

Sulfatides (ST) are glycosphingolipids composed of ceramide, galactose, and sulfate. They are expressed in many organs such as the brain, kidney, liver, heart, intestine, muscle, and pancreas (Kyogashima 2004; Hara et al. 1993). Together with galactosylceramides, STs are crucial myelin lipids required for the stability and maintenance of the myelin sheet (Schmitt et al. 2015). They are also expressed in neurons and astrocytes of the gray matter of the brain (Pernber et al. 2002; Isaac et al. 2006; Blomqvist et al. 2017). Sulfatides contribute to a variety of cellular processes including protein trafficking, cell adhesion, aggregation, and immune responses (Xiao and Finkielstein 2013). Sulfatide release from myelin is associated with the development of neurological diseases such as early Alzheimer's disease (Cheng et al. 2013), as the presence of ST in the cerebrospinal fluid might serve as a marker of demyelination, myelin damage, and myelin turnover (Cheng et al. 2013; Blomqvist et al. 2017). It is known that chronic drug consumption, e.g., alcoholism, causes neurodegeneration with major impairment in the structural integrity of myelin (Yalcin et al. 2017). Thus, the investigation of sulfatide involvement in the development of drug dependence is recently of specific interest.

## Alcohol

A study by Yalcin et al. (2015) revealed a decrease in the content of ST18:0, ST24:0, ST24:1 and PI36:4, PI36:1; PI38:4, PI38:3 phosphatidylinositols in the brain of rats receiving alcohol p.o. and i.p. in an 8-week protocol (Yalcin et al. 2015). Middle and high doses, but not low-dose alcohol treatment significantly reduced serum and liver ST levels via down-regulation of cerebroside sulfotransferase (CST) activity in the liver. CST is a key enzyme of ST synthesis catalyzing the final step in the synthesis by transferring the sulfate from 3'-phosphoadenosine 5'-phosphosulfate to galactocerebroside. CST mRNA levels were reduced by the middle- and high-dose alcohol, but not by low-dose alcohol treatment. However, mRNA of arylsulfatase A, an enzyme catalyzing ST degradation, was not affected by alcohol in any of the study doses. The authors suggest that the pronounced decrease in the expression of catalase and superoxide dismutases and increase in the intensity of lipid peroxidation in the liver of alcohol-treated mice are associated with CST suppression in the liver (Kanbe et al. 2014). These data might suggest an interaction between various pathways of alcohol use disorder, such as oxidative stress and alterations in the SL systems. Altogether, a decrease in ST levels in the brain of alcohol-treated mice might reflect neurodegenerative processes. However, these changes are not in line with a reduction in ST concentration in the peripheral tissues, as demyelination processes is often associated with an increase in peripheral ST. Further investigation of these changes is needed.

## Nicotine

Administration of nicotine-derived nitrosamine ketone induced a decrease in the expression of ST24:0 and ST24:1(OH) in the corpus callosum, cortex, and hypothalamus of rats. This decrease correlated with white matter demyelination or hypo-myelination. The authors suggested that nicotine-derived nitrosamine ketone-induced axonal loss is mediated by the reduction in ST concentration in those brain structures (Yalcin et al. 2015). These data provide evidence for a contribution of STs to the toxic effects of cigarette smoking, particularly smoking-induced neuroapoptosis. Altogether, these data indicate that ST is particularly important for neurodegenerative processes induced by drug consumption. Further investigations of this pathway of neuron demyelination should be performed to understand if modulation of ST concentration might be used for the prevention of drug-induced neurodegeneration associated with cognitive impairment.

## Cerebrosides

Cerebrosides constitute a family of neutral glycosphingolipids containing a 3-*O*-acetyl-sphingosine galactosylceramide consisting of two main subgroups—galactosylceramides and glucosylceramides. They are the most abundant glycolipid components of myelin enriched in both central and peripheral nervous system myelin. The average GalCer concentration is around 20% for the central and around 30% for the peripheral nervous system (Dasgupta et al. 2002; Podbielska et al. 2011).

## Alcohol

An increase in the levels of cerebroside, glucosylceramide, lactosylceramide, and globotriaosylceramide was found in microvilli membranes of the intestine of rats chronically fed with alcohol for 35 or 56 days (Grewal and Mahmood 2010). The authors suggested that an increase in the concentrations of these SLs in the intestine of rodents might be related to the dystrophic changes in the intestinal epithelium typical for alcohol consumers. Long-term exposure to alcohol resulted in extensive mucosal damage, including thinning of brush borders, shortening of villi, and reduced mucosal surface in the intestine (Bode and Bode 2003; Peres et al. 2004). Moreover, alcohol consumption was associated with a compromised immune status of the intestine and an increased incidence of general infection by facilitation of bacterial passage through the intestinal epithelium (Bode and Bode 2003). These changes in the immune status of epithelial cells of the intestine are considered to be at least partly mediated by increased levels of ceramides, which form an activating loop with pro-inflammatory cytokines such as IL-6 and TNF- $\alpha$  (Józefowski et al. 2010; Hamada et al. 2014; Gomez-Muñoz et al. 2016). These data suggest an involvement of cerebroside in the peripheral toxic effects of alcohol.

## Conclusions

In summary, numerous studies in recent years revealed new pathogenesis pathways involved in the action of addictive drugs. It was shown that SLs are tightly involved in the pathogenesis of addictive disorders. As such, they might be interesting as novel targets for the treatment of this disease. One of the most important findings is related to the apoptotic neurodegeneration typical for many addictive drugs. Especially, for alcohol use disorder, this seems to be determined by SLs. Particularly, ceramides and gangliosides mediate the imbalance of neuronal death and proliferation induced by psychoactive substances. Single investigations pointed out a role of SLs in plastic processes in the brain that are required for the normal development of drug-related behavior.

Interestingly, an increasing number of studies showed dual properties of SLs during moderate alcohol consumption and revealed beneficial effects of these lipids in the central nervous system. These data allow proposing that SLs contribute to the specific type of controlled consumption of psychoactive substances named drug instrumentalization, in which beneficial and adverse effects of a drug can still be balanced (Müller and Schumann 2011a, b). However, during long-term intake of addictive drugs, these classes of lipids might also play a role in the transition to addiction, where adverse drug effects dominate.

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### Compliance with ethical standards

**Conflict of interest** The authors declare no competing financial interests.

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