Lipids and synaptic functions

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Abstract
Synaptic functions have long been thought to be driven by proteins, especially the SNARE complex, contrasting with a relatively passive role for lipids constituting cell membranes. It is now clear that not only lipids, i.e. glycerophospholipids, sphingolipids and sterols, play a determinant role in the dynamics of synaptic membranes but they also actively contribute to the endocytosis and exocytosis of synaptic vesicles in conjunction with synaptic proteins. On the other hand, a growing number of inborn errors of metabolism affecting the nervous system have been related to defects in the synthesis and remodelling of fatty acids, phospholipids and sphingolipids. Alterations of the metabolism of these lipids would be expected to affect the dynamics of synaptic membranes and synaptic vesicles. Still, only few examples are currently documented. It remains to be determined to which extent the pathophysiology of disorders of complex lipids biosynthesis and remodelling share common pathogenic mechanisms with the more traditional synaptopathies.

Role of lipids in synaptic functions

Lipids can be subdivided into simple lipids such as fatty acids (FA), sterols and acylglycerols, and complex lipids such as glycerophospholipids, ether phospholipids and sphingolipids (Fahy et al. 2005). The fatty acyl group from FA and conjugates is made of a repeating series of methylene bridges rendering them hydrophobic. The fatty acyl structure is the major lipid backbone of complex lipids. Glycerolipids result from the link between FA and a glycerol backbone through ester bounds and encompass all glycerol-containing lipids. They include glycerophospholipids (phosphatidyl-choline, -ethanolamine, -serine and -inositol) and glycerolipids (mono, di and triacylglycerol). Phospholipids are made of a glycerol molecule, two FA and a phosphate group that is modified by an alcohol. The phosphate group is hydrophilic due to its negatively charged polar head, while the FA chains are hydrophobic due uncharged, non-polar tails (Fahy et al. 2005). Triacylglycerols differ from glycerophospholipids as they carry a third ester bound acyl chain instead of the phosphate group, making them completely hydrophobic (Fahy et al. 2005). Sphingolipids share a common structural feature, a sphingoid base backbone that is synthesised de novo from serine and a long chain fatty acyl-CoA. The sphingoid bases are acylated with a FA in order to form ceramide, which can carry a hydrophilic head group, e.g. phosphorylcholine in the case of sphingomyelin or carbohydrate residues in the case of glycosphingolipids (Fahy et al. 2005). Most of these major lipid classes, e.g. phospholipids, sphingolipids and sterols, contain a wide range of metabolic and molecular species that differ in polar head and hydrophobic tail groups, phosphorylation states and regulation by kinases and phosphatases. Therefore, the signalling and regulatory potential of lipids is wide. Synaptic membranes are especially abundant in glycerophospholipids, sphingolipids and cholesterol.

The key role of lipids in synaptic functions is mediated by their implication in the dynamics of synaptic membranes and synaptic vesicles (Rohrbough and Broadie 2005; Piomelli et al. 2007; Lauwers et al. 2016). Lipid composition and topology is indeed an important factor in the spatial regulation of membrane shape, curvature and fluidity during vesicle fusion (exocytosis) and fission (endocytosis). Let us first consider the

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role of lipids in the dynamics of synaptic membranes. Due to their physic properties, lipids directly control membrane biophysical parameters such as curvature, fluidity and thickness. Indeed, the geometry of membrane lipids depends on the area occupied by the head group versus the hydrophobic part of the molecule. Cone-shaped lipids (ceramide, phosphatidic acid, diacylglycerol, phosphatidylethanolamine) have a small head group and promote negative membrane curvature. Conversely, lipids like phosphatidylcholine have a nearly cylindrical geometry, while lysophosphatidylcholine has an inverted cone shape. Likewise, presynaptic lipid bilayers undergo extensive and concerted shape changes as they transit through the different lipid shapes (cone, cylinder, inverted cone). These changes are driven by phospholipases, e.g. deacylation of phosphatidylcholine (cylinder) into lysophosphatidylcholine (inverted cone) by phospholipase A2 (Lauwers et al. 2016). Hence, remodelling of membrane phospholipids by phospholipases is crucial for synaptic function and maintenance as it directly affects membrane curvature but also permits the release of lipid signalling molecules like arachidonic acid by phospholipase A2 or diacylglycerol by phospholipase C.

Let us now consider the role of lipids in endocytosis and exocytosis of synaptic vesicles. Presynaptic endocytosis and synaptic vesicle release are linked in time and space. Several proteins involved in the priming and docking of synaptic vesicle bind lipids that are negatively charged, e.g. phosphatidylinositol phosphates, in order to cluster in the active zone where exocytosis takes place (Lauwers et al. 2016). Many of these proteins recognise only one given phosphatidylinositol phosphate species (Hammond and Balla 2015). Therefore, the phosphatidylinositol phosphates-composition of a membrane determines which proteins are recruited, a process that has been well characterised in the endosomal system (Di Paolo and De Camilli 2006). Phosphatidylinositol phosphates are also inter-converted by specific kinases and phosphatases. These enzymes are determinant to generate rapid changes in the membrane concentration of phosphatidylinositol phosphates so that the endocytic machinery can be sequentially recruited for the formation of synaptic vesicles (Ueda 2014). Hence, phosphatidylinositol phosphates and their metabolising enzymes help coordinate endocytosis, via the sequential recruitment and subsequent disassembly of membrane-remodelling proteins. Furthermore, the exocytosis of synaptic vesicles requires membrane fusion between the synaptic vesicle and plasma membrane. This process is mediated by the assembly of SNARE complexes (especially synaptobrevin, syntaxin and SNAP-25) and is assisted by cone-shaped, also called fusogenic, lipids and membrane-remodelling proteins. Likewise, phosphatidylinositol phosphates, but also phosphatidylserine (Williams et al. 2009), promote the binding of synaptobrevin and syntaxin by shielding positive charges on either protein as they approach each other during synaptic vesicle docking. Besides, polyunsaturated FA (PUFA) can induce a conformational change on syntaxin favouring its interaction with SNAP-25 (Darios et al. 2007) while sphingosine mediates the relief of the cytoplasmic part of synaptobrevin, which is necessary for its interaction with the syntaxin/SNAP-25 heterodimer (Darios et al. 2009). Altogether, by regulating interactions between charged domains of the SNARE machinery, glycerophospholipids, sphingolipids and PUFA play an active role in exocytosis. Other lipids such as diacylglycerol and phosphatidic acid have a direct role in the regulation of synaptic vesicle exo/endocytosis (Tu-Sekine et al. 2015). Thus, diacylglycerol acts on priming of syntaxin for SNARE-mediated vesicle fusion (Wierda et al. 2007).

It is noteworthy that cholesterol impacts both the dynamics of synaptic membranes and synaptic vesicles. Together with sphingolipids, cholesterol is indeed essential for raft integrity and function. Still, only cholesterol has the unique ability to engage in rapid trans-bilayer flip-flop, allowing for stress relaxation during membrane bending and thereafter membrane remodelling (Bruckner et al. 2009). On the other hand, cholesterol is enriched in secretory and synaptic vesicles and is important for neurosecretory and synaptic vesicle cycling and release (Rohrbough and Broadie 2005). Indeed, syntaxins are concentrated in cholesterol-dependent clusters at which secretory vesicles preferentially dock and fuse (Lang et al. 2001). Cholesterol also binds the synaptic vesicle protein synaptophysin in order to modulate its interaction with synaptobrevin (Mitter et al. 2003). The cholesterol–synaptophysin–synaptobrevin interaction is thought to recruit and segregate essential synaptic vesicle-specific proteins from the plasma membrane (Thiele et al. 2000).

Neurometabolic diseases caused by defects in the synthesis or remodelling of complex lipids

Defects in lipid catabolic pathways have been involved for decades in numerous inborn errors of metabolism (IEM), especially lysosomal storage diseases and peroxisome biogenesis disorders. These catabolic defects lead to the accumulation of lipid substrates that have become useful diagnostic biological markers such as lysosphingolipids (Pettazzoni et al. 2017) and C26:0- lysophosphatidylcholine (Klouwer et al. 2017). Conversely, IEM related to defects in the biosynthesis and remodelling of glycerophospholipids, sphingolipids and fatty acids have only been delineated recently (Lamari et al. 2013) but rapidly expanded to over 100 diseases (Lamari et al. 2015) thanks to the increased access to next-generation sequencing tools. Diagnostic biological markers are still missing for this large group of IEM of diseases as decrease in product is

usually more difficult to detect than substrate accumulation, and even more so with lipid species that are very redundant such as glycerophospholipids. Still, the measurement of several hundreds of lipid species using lipidomics may allow a better delineation of some of these metabolic defects (Seyer et al. 2016). The clinical presentation of IEM involved in the synthesis and remodelling of complex lipids has been reviewed in details (Garcia-Cazorla et al. 2015). All organs and systems may be affected—the central and peripheral nervous system, eye, muscle, heart, skin, bone, liver and immune system. We will focus here on IEM primarily affecting the nervous system and presenting with a combination of intellectual disability, epilepsy, movement disorder, sensorineural dysfunction, peripheral neuropathy and/or myopathy.

A first category of IEM relates to defects in the synthesis of phospholipids (Fig. 1). ABHD5 is α/β-hydrolase domain-containing 5 that acts as a lysophosphatidic acid acyltransferase and therefore plays a role in the synthesis of phosphatidic acid (Fig. 1). Its defects cause Chanarin-Dorfman syndrome, a neutral lipid storage disease characterised by intellectual disability, cerebellar ataxia and myopathy associated with cataract, hearing loss, erythrodermic ichthyosis and hepatomegaly with liver steatosis (Lefèvre et al. 2001). Phosphatidic acid can be converted into diacylglycerol by a phosphatidic acid phosphatase called Lipin 1 (Fig. 1). Defect in Lipin-1 is the most common cause of rhabdomyolysis after FA oxidation disorders, and episodes are usually induced by fever, anaesthesia or fasting (Zeharia et al. 2008). Choline kinase b (CHB) catalyses the first step in the de novo biosynthesis of phosphatidylcholine (Fig. 1). CHB deficiency causes intellectual disability, epilepsy, early onset muscular dystrophy and dilated cardiomyopathy (Mitsuhashi et al. 2011). PCYT1A encodes the α-isoform of phosphate cytidylyltransferase 1 choline, which is responsible for converting phosphocholine into cytidine diphosphate-choline, a key intermediate step in the phosphatidylcholine biosynthesis pathway (Fig. 1). Defect in PCYT1A causes a cone-rod dystrophy associated with a spondylometaphyseal dysplasia (Hoover-Fong et al. 2014). Phosphatidylserine synthase 1 (PSS1) synthesises phosphatidylserine through the exchange of L-serine with the choline moiety of phosphatidylcholine (Fig. 1). PSS1 deficiency is responsible for the autosomal dominant Lenz-Majewski syndrome that is characterised by intellectual disability, *cutis laxa* and a sclerosing bone dysplasia with hyperostotic dwarfism (Sousa et al. 2014).

The second category of IEM relates to the remodelling of phospholipids (Fig. 2). SERAC1 is involved in remodelling phosphatidylglycerol-34:1 to phosphatidylglycerol-36:1 species, the latter being the precursor for bismonoacylglycerophosphate (BMP) and cardiolipin species (Fig. 1). Defect in SERAC1 causes MEGDEL (3-MEthylGlutaconic aciduria with deafness, encephalopathy and Leigh-like) syndrome, characterised by intellectual disability, deafness, dystonia and spasticity (Wortmann et al. 2012). An alternative pathway for diacylglycerol and FA synthesis is their release from membrane phospholipids by specific phospholipases and lysophospholipases (Fig. 2). PLA2G6 is a phospholipase A2 that removes unsaturated FA chains and arachidonic acid, which is the starting molecule of many complex FA like prostaglandins, leukotrienes (Fig. 2). *PLA2G6* mutations are associated with three phenotypes: INAD (infantile neuroaxonal dystrophy) that causes psychomotor regression, spasticity, peripheral neuropathy and optic atrophy; NBIA (neurodegeneration with brain iron accumulation) that causes cerebellar ataxia, dystonia and psychiatric symptoms; and a dystonia-parkinsonism syndrome (Paisan-Ruiz et al. 2009; Illingworth et al., 2014). DDHD1 and DDHD2 are phospholipase A1 that remove saturated FA chains (Fig. 2). DDHD2 is also a triglyceride lipase. Mutations in *DDHD1* and *DDHD2* are associated with complex forms of spastic paraplegia—i.e. pigmentary retinopathy and intellectual disability, respectively (Tesson et al. 2012; Schuurs-Hoeijmakers et al. 2012). NTE (neuropathy target esterase) is a patatin-like phospholipase that has a lysophospholipase activity, releasing glycerophospholipids (Fig. 2). *NTE* mutations have been associated with a large spectrum of neurological disorders—spastic paraplegia 39, Gordon Holmes syndrome, Boucher-Neuhauser syndrome, Olivier McFarlane syndrome and Laurence-Moon syndrome—that have in common spastic paraplegia, cerebellar ataxia, chorioretinal dystrophy and hypogonadism (Synofzik et al. 2014). CYP2U1 is a cytochrome P450 that catalyses the hydroxylation of arachidonic acid and similar long-chain FA, leading to the formation of hydroxyeicosatetraenoic acids (Fig. 2). *CYP2U1* mutations cause spastic paraplegia, which can be associated with intellectual disability, dystonia, peripheral neuropathy and pigmentary maculopathy (Tesson et al. 2012). Phospholipase C removes phosphate groups and leads to the release of diacylglycerol and its further conversion by diacylglycerol lipase into 2-arachidonoyl glycerol, which can then be hydrolysed into arachidonic acid by α/β-hydrolase-12, ABHD12 (Fig. 2). *ABHD12* mutations are associated with PHARC syndrome, characterised by peripheral neuropathy, hearing loss, cerebellar ataxia, pigmentary retinopathy and cataract (Fiskerstrand et al. 2010) or an isolated pigmentary retinopathy (Nishiguchi et al. 2014).

The third category of IEM relates to the synthesis of sphingolipids (Fig. 3). Serine palmitoyltransferase catalyses the condensation of palmitoyl-CoA and L-serine to generate ketosphinganine, which is then reduced to sphinganine. This is the first and rate limiting step in the de novo synthesis of sphingolipids. *SPTLC1* and *SPTLC2* mutations cause an autosomal dominant sensory and autonomic neuropathy due to

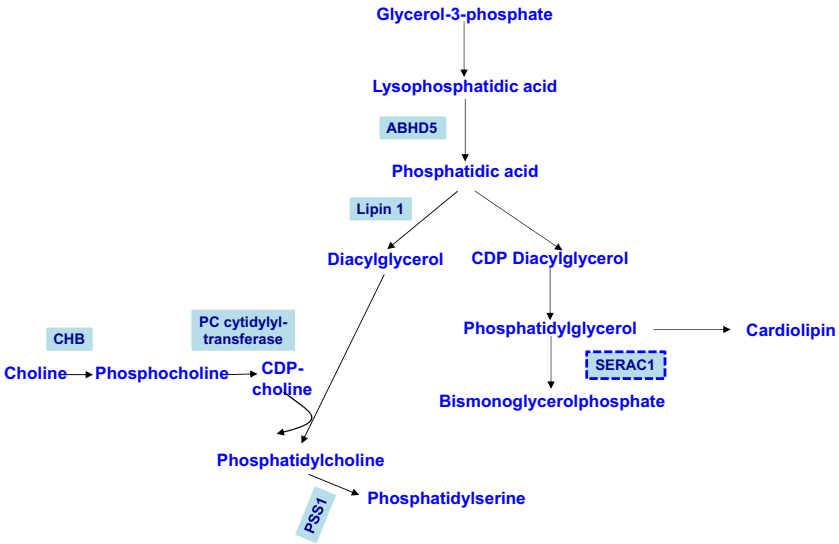

Fig. 1 Phospholipids biosynthetic pathways—selected steps (modified from Lamari et al. 2015). ABHD5 α/β-hydrolase domain-containing 5, CHB choline kinase b, PCYT1A α-isoform of phosphate cytidylyltransferase 1 choline, PSS1 phosphatidylserine synthase 1. Dashed boxes represent remodelling steps

the abnormal production of toxic ceramides (Rotthier et al. 2010). Fatty acid 2 hydroxylase (FA2H) introduces a hydroxyl group at the C2-position of FA. The corresponding hydroxylated fatty acyl-CoA is incorporated by ceramide synthases (CERS) into sphingolipids (Fig. 3). *FA2H* mutations have been associated with a spectrum of spastic paraplegia (SPG35), intellectual disability, epilepsy, dystonia, white matter disease and NBIA (Kruer et al. 2010). *CERS2* mutations were found in the Amish population causing progressive myoclonic epilepsy (Mosbech et al. 2014). GBA2 encodes the glucocerebrosidase that is mainly expressed in the endoplasmic reticulum and can produce ceramide from glucosylceramide (Fig. 3). *GBA2* mutations are responsible for a spastic ataxia often associated with intellectual disability, axonal neuropathy, cataract and/or hearing loss (Martin et al. 2013; Hammer et al. 2013). GM3 synthase catalyses the formation of GM3 gangliosides using lactosylceramide as the substrate. Deficiency in GM3 synthase causes an early onset epilepsy associated with intellectual disability, choreoathetosis, optic atrophy and hyperpigmented lesions (Simpson et al. 2004). *B4GALNT1* encodes β-1,4-N-acetylgalactosaminyltransferase 1, that synthesises GM2 and GD2 gangliosides. *B4GALNT1* mutations lead to intellectual disability, cerebellar ataxia, dystonia, muscle wasting and axonal neuropathy (Boukhris et al. 2013).

Abnormal lipid metabolism and synaptic dysfunction?

How to reconcile this expanding list of IEM affecting the biosynthesis and remodelling of glycerophospholipids, sphingolipids and fatty acids with the key role of lipids in synaptic function? One can indeed hypothesise that the altered production of glycerophospholipids (e.g. phosphatidylcholine, phosphatidylserine, phosphatidylinositol phosphates) or their precursors (e.g. phosphatidic acid, diacylglycerol), PUFA (e.g. arachidonic acid) or sphingolipids (e.g.

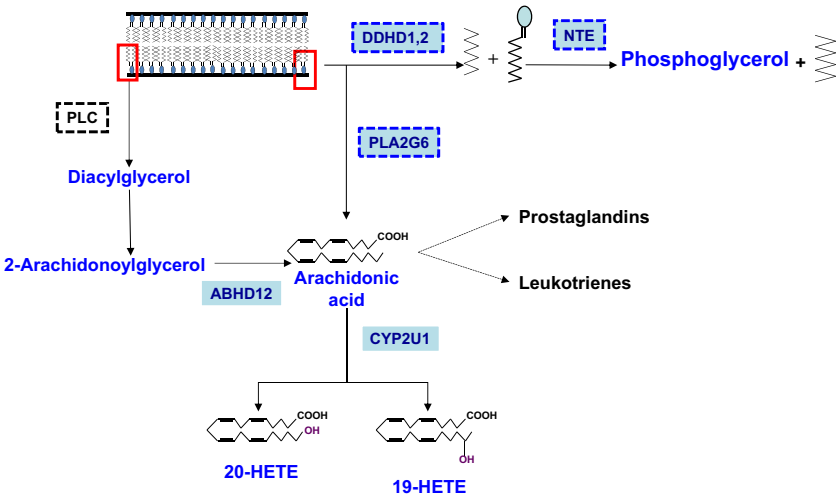

Fig. 2 Phospholipids remodelling pathways—selected steps (modified from Lamari et al. 2015). PLA2G6 phospholipase A2 group VI, NTE neuropathy target esterase, ABHD12 α/β-hydrolase-12, HETE hydroxyeicosatetraenoic acids, PLC phospholipase C. Dashed boxes represent remodelling steps

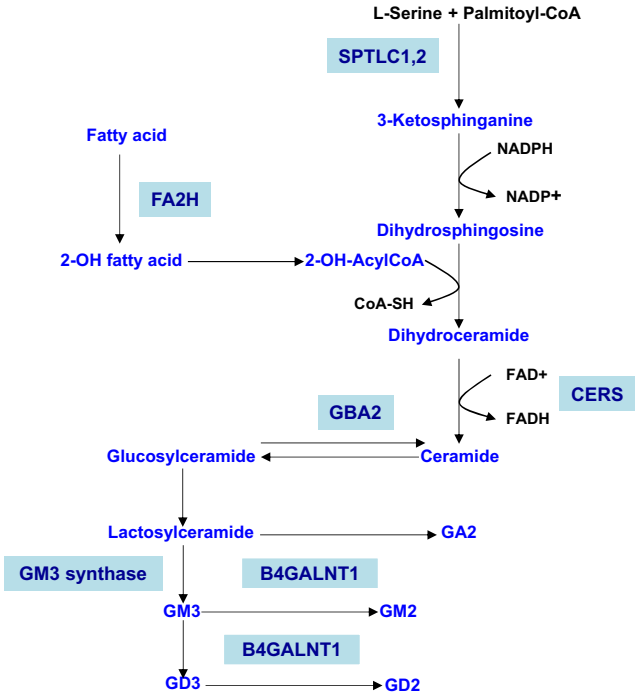

Fig. 3 Sphingolipids biosynthetic pathways—selected steps. SPTLC 1/2 serine palmitoyltransferase1/2, F FA2H fatty acid 2 hydroxylase, CERS ceramide synthase, GBA2 glucocerebrosidase type 2, B4GALNT1 β-1,4-N-acetyl-galactosaminyltransferase 1

sphingosine, ceramide) would affect membrane curvature and the dynamics of synaptic membranes, as well as the formation of synaptic vesicles and their release. Likewise, loss of function of PLA2G6, which catalyses the deacylation of phosphatidylcholine with release of unsaturated FA chain and regulates membrane remodelling, has been associated with presynaptic membrane defects (Sumi-Akamaru et al. 2015). Furthermore, loss of function of phosphatidylinositol phosphates metabolising enzymes have been associated with several neurodegenerative disorders. Mutations in *PIP5K1C*, which encodes an enzyme that phophorylates phosphatidylinositol 4-phosphate to generate phosphatidylinositol-4,5-bisphosphate, and mutations in *ERBB3*, which encodes an activator of the phosphatidylinositol-3-kinase, cause lethal congenital contracture syndromes with atrophy of the anterior horn of the spinal cord (Narkis et al. 2007a; Narkis et al. 2007b). Synaptojanin, encoded by *SYNJ1*, is a phosphatidylinositol phosphate phosphatase. *SYNJ1* mutations in the SAC1 domain that dephosphorylates phosphatidylinositol 3-phosphate and phosphatidylinositol 4-phosphate, found on synaptic vesicle membranes, causes early onset Parkinson's disease and epilepsy (Krebs et al. 2013).

Altogether, both pre- and postsynaptic effects of altered lipid metabolism ought to have an impact on the development of neurological disorders. Similarly to IEM affecting lipid metabolism, diseases caused by defects in proteins involved in synaptic functions, traditionally called synaptopathies, encompass epilepsy, intellectual disability, movement disorders, cerebellar ataxia, spastic paraplegia, peripheral neuropathy and myopathy (Cortès-Saladelafont et al. 2016). Therefore, it remains to be determined to which extent the pathophysiology of IEM affecting the biosynthesis and remodelling of glycerophospholipids, sphingolipids and fatty acids is related to synaptic dysfunction and share common pathogenic mechanisms with these synaptopathies.

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Compliance with ethical standards

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Conflict of interest Fanny Mochel declares that she has no conflict of interest.

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