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Membrane lipid domains in the nervous system

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1. ABSTRACT

The structural properties of the lipids forming biological membranes determine a very high level of lateral organization within membranes. Lipid-driven membrane organization allows the segregation of membrane-associated components into membrane lipid domains, now worldwide known as lipid rafts, acting as dynamic platforms for signal transduction, protein processing and membrane turnover. Many processes necessary to the correct functions of nervous system occur in lipid rafts and *are dependent on lipid raft organization. Thus, an altered lipid composition frequently occurring in neurodegenerative diseases leads to anomalous lipid raft organization and then to deregulated cell signaling.*

2. BIOLOGICAL MEMBRANES AND LIPID RAFTS

The collective and physic-chemical properties of membrane lipids, namely cholesterol, glycerophospholipids (GPL) and sphingolipids (SL), are the starting point for the membrane existence but also drive the formation of highly organized multimolecular structures and lead to the creation of multiple and multi-dimensional levels of order (1, 2). Thanks to their hydrophobic nature, lipid bilayers accept lipophilic proteins, increasing the complexity of chemical interactions occurring in biological environments. Due to the fatty acyl chains of the glycerophospholipids, the main structural lipids in the membrane, that at physiological temperatures are in a fluid phase, lipid bilayers behave as two-dimensional fluids. Thus, proteins dissolved in this 2D hydrophobic film possess a relatively high degree of lateral motility allowing their distribution along the membrane surface in a random arrangement (3-5).

Biological membranes provide the matrices for the organization of complex multimolecular interactions, that need to be highly dynamic in time and space: they need to transduce signals along the membrane plane and they need to acquire a variety of geometries within the same cell to form distinct and morphologically distinguishable “micro” domains. This requires the existence of lateral interactions among membrane components able to stabilize different substructures with their own local order, that differ in lipid and/or protein composition from the surrounding membrane environment (6). Proteins possess a very high potential for the creation of multimolecular interactions, and differential sorting of specific subset of proteins to specialized membrane regions leads to specific protein-protein interactions and specific biological processes (7).

Membrane lipids account for hundreds of different molecular species (8-10), whose expression, sorting and turnover is tightly regulated along development and activation in different cell types. The highest level of structural complexity is evident for SL and in particular for glycosphingolipids (GSL), characterized by great heterogeneity in both their ceramide-based hydrophobic moiety (11-14) and hydrophilic head groups (9). Noteworthy, the expression of a developmentally regulated cell specific lipid pattern (as it occurs for SL in the nervous system (15)) requires the intervention of a complex set of biosynthetic and catabolic enzymes (16, 17), and the involvement of an extremely complex traffic

and sorting machinery (18, 19). Thus, it is not surprising that the aggregative and cooperative properties of the membrane complex lipid mixtures can play a relevant role as a driving force for the creation of lateral order and of local organization within cell membranes (20-23). Lipids in complex lipid mixtures possess a limited solubility, which leads to fluid-fluid phase separation (this information is now quite old (24)). Features leading to phase separation in lipid mixtures can be described as collective behavior in different ways, however they basically consist in molecular mismatches between the lipid components of a certain mixture. In mixtures of amphipathic lipids with the same or very similar polar head groups, molecular mismatches can be due to different composition of their hydrophobic moieties (25). The structure of the hydrophobic moiety is the main determinant for differences in the chain melting temperature, which in turn can drive phase separation in lipid mixtures, leading to spatial separation of domains with different fluidity (26-28). Considering that GPL containing unsaturated acyl chains are prevalent, and that a membrane bilayer is more fluid if the constituent lipid has unsaturated hydrophobic chains, biologically lipid bilayers under physiological conditions usually exist in a liquid-disordered (l*d*) phase characterized by high fluidity, in which the lipid acyl chains are disordered and highly mobile. The degree of order of the hydrophobic chains increases (and their freedom of movement decreases) by lowering the temperature and freezing the bilayer in an ordered gel phase (solid-ordered). However, in some tissues and cell types (e.g., in brain and in neurons) glycero- and sphingolipids with saturated chains (mainly palmitic acid) are relatively abundant (29-31), and, in the case of sphingomyelin and of gangliosides, prevalent (31). Moreover, all eukaryotic cell membranes contain significant or in some cases, relevant amounts of cholesterol, a lipid with a very high melting temperature (cholesterol represents about 7, 15 and 20%, respectively, of dry weight in grey matter, white matter and myelin from adult human brain (32); cholesterol in differentiated rat cerebellar neurons is about 12% of their total lipid content (29, 33). In mixtures comprising a bilayer-forming lipid, such as dipalmitoylphosphatidylcholine, and cholesterol, a third physical phase, the liquid-ordered (l*o*) phase (34-37), can exist. In the l*o* phase, the acyl chains of lipids are extended and ordered, as in the solid phase, but have higher lateral mobility in the bilayer. Cholesterol stabilizes the l*o* phase, because it is able to closely interact via its smooth and planar α-face with the ordered acyl chains of l*o* phase lipids, thus filling in the hydrophobic gaps between the acyl chains. Sphingolipids in lipid bilayers are intrinsically prone for phase separation and partition to l*o* phase due to several molecular features (1, 2, 36, 38). The saturated fatty acyl chains prevalent in some sphingolipid classes (such as sphingomyelin and gangliosides) are extended and ordered in the core of the lipid bilayer, and can tightly interact with cholesterol (39). In addition, clustering of sphingolipids is further driven by the formation of a complex network of hydrogen bonds (40, 41) allowed by the presence in the ceramide moiety of the amide proton, the carbonyl oxygen and the hydroxyl group positioned in proximity of the water/lipid interface of the bilayer (42). Moreover, in the case of glycosphingolipids, their sugar hydrophilic portions of various complexity represent a further element of molecular mismatch and a further driving force for segregation, due to their bulkiness and to the possibility to establish strong orientated correlations in the oligosaccharide clusters.

The concept on lipid rafts became popular following the suggestion that the different lipid composition of the apical and basolateral plasma membranes of polarized epithelial cells could be due to the self-associative properties of sphingolipids and cholesterol enriched in the apical domain (43, 44). Later, the lipid raft hypothesis was generally accepted (45) and an incredible number of papers are available describing specific subset of proteins and of biological functions associated with lipid rafts, even if along the years a number of controversial issues has been raised regarding the analytical aspects relative to the study of lipid rafts, the real nature, the size, lifespan, dynamics and even the actual existence in living cells of these structures. Nevertheless, new technical approaches are allowing to progressively overcome some of the above issues (46-48).

3. LIPID RAFTS IN THE NERVOUS SYSTEM

The brain is the tissue with the highest content of complex lipids, in the human body (49). In particular, neural cells are the richest in sphingolipids, and particularly in glycosphingolipids, that represent very minor components of cells outside the nervous system. Brain gray matter and neurons are highly enriched in gangliosides, sialic-acid containing GSL, and are characterized by a very high complexity and heterogeneity of molecular species (50) (Table 1 and Figure 1). Myelin and oligodendrocytes are highly enriched in the galactolipids galactosylceramide and

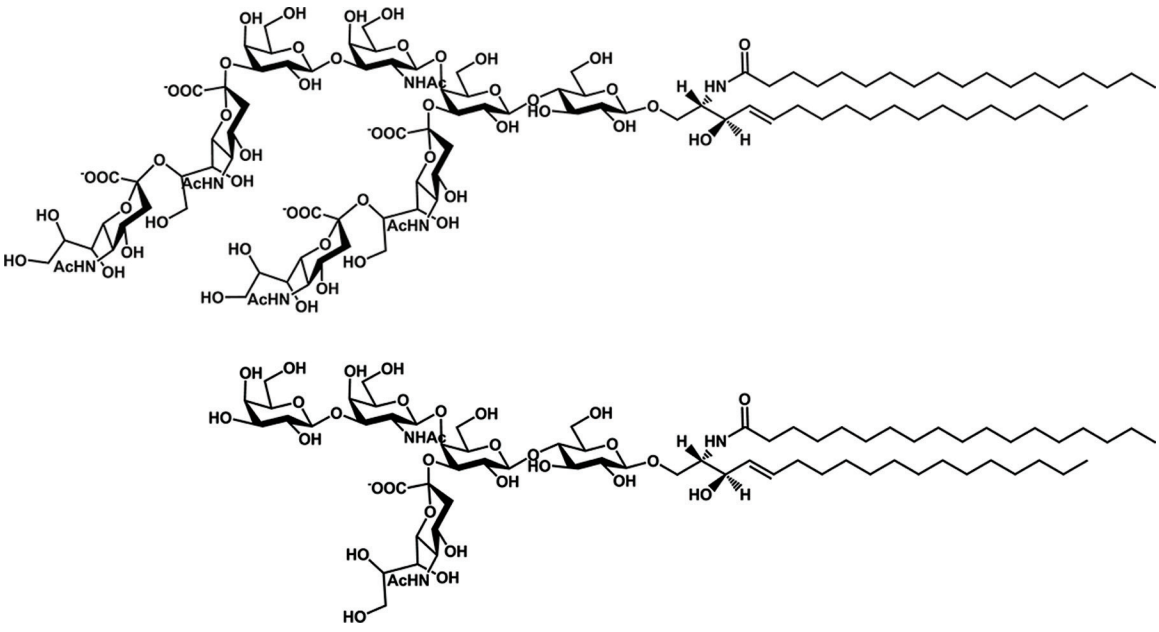

Figure 1. Structure of GQ1b and GM1 gangliosides. The figure reports the structure of two main gangliosdes of the plasma membranes of neurons. They belong to the gangliotetrahexosyl series characterized by the neutral oligosaccharide chain ß-Gal-(1-3)-ß-GalNAc-(1-4)-ß-Gal-(1-4)-ß-Glc- linked to ceramide. 2 disialyl chains are linked to the position 3 of inner and external galactose in GQ1b. One sialic acid residue is linked to the position 3 of inner galactose in GM1.

sulfatide, and in sphingomyelin (51, 52). Brain cells are rich in cholesterol (53, 54), and are extremely avid for essential fatty acids (55). In brain, non-conventional lipid mediators such as oxysterols and cannabinoids are also present (56).

It is now accepted that lipid rafts with their specific subsets of signaling proteins are responsible for the regulation of signal transduction cascades. Usually the preferential association of a certain protein with lipid rafts is determined by structural features that can act as raft-targeting domains, like a GPI anchor, cysteine S-palmitoylation, N-myristoylation/palmitoylation and double palmitoylation (57), or by the presence of a binding motif for cholesterol or for a sphingolipid, like that present in α-synuclein, β-amyloid peptide, serotonin(1A) receptor and nicotinic acetylcholine receptor (39, 58, 59). The list of lipid raft-associated proteins involved in different aspects on nervous system function is growing (Table 2), and encompasses for receptor tyrosine kinases (60-64), non-receptor tyrosine kinases of the Src family (65-67), adapter and regulatory molecules of tyrosine kinase signaling (68), heterotrimeric and small GTP-binding proteins (69, 70), cell adhesion molecules (66, 71-73) and postsynaptic density complex proteins (64, 74-76).

The localization of proteins within a membrane with a high degree of lateral order has direct important consequence of the tri-dimensional structure of the protein, and the co-localization of different proteins into the same lipid rafts favors their reciprocal interactions. In addition, concentration of a protein into a lipid rafts increases the chance of establishing protein-lipid interactions with functional significance. GSL, with their complex oligosaccharide head groups, are able to engage lateral interactions with membrane-associated proteins, which can in principle involve amino acid residues belonging the extracellular domain of the protein, the glycan of a glycosylated protein, or even the hydrophilic portion of a GPI anchor. The inhibitory effect exerted by GM3 ganglioside on EGFR autophosphorylation is mediated by a side-by-side lateral interaction between the GM3 oligosaccharide chain and a GlcNAc-rich motif in the terminal region of an N-linked glycan borne by the receptor (77, 78). A similar raft-dependent lateral interaction is likely involving GM1 ganglioside, and possibly other ganglio-series structures, and neurotrophin receptors belonging to the Trk family. GM1 is able to exert positive effects on neuronal survival, neurite outgrowth, and in general neuronal differentiation both *in vivo* and in cultured

Table 1. The main gangliosides from human brain

Oligosaccharide chain	Series
ß-Gal-	Gal
ß-Gal-(1-4)-ß-Glc-	Lac
ß-GalNAc-(1-4)-ß-Gal-(1-4)-ß-Glc-	Gg_3
ß-Gal-(1-3)-ß-GalNAc-(1-4)-ß-Gal-(1-4)-ß-Glc-	Gg_4
ß-GalNAc-(1-4)-ß-Gal-(1-3)-ß-GalNAc-(1-4)-ß-Gal- (1-4)-ß-Glc-	Gg_5
Acidic glycosphingolipid nomenclature (1)	
Nomenclature and structure	
SM4s,-O_3SGalCer	-O_3S-3-β-Gal-(1-1)-Cer
GM4, Neu5AcGalCer	α-Neu5Ac-(2-3)-ß-Gal-(1-1)-Cer
GM3, II^{3}Neu5AcLacCer	α-Neu5Ac-(2-3)-ß-Gal-(1-4)-ß-Glc-(1-1)-Cer
GD3, II^3(Neu5Ac)$_2$LacCer	α-Neu5Ac-(2-8)-α-Neu5Ac-(2-3)-ß-Gal-(1-4)-ß-Glc-(1-1)-Cer
GM1, II^{3}Neu5AcGg$_4$Cer	β-Gal-(1-3)-ß-GalNAc-(1-4)-(α-Neu5Ac-(2-3)-) ß-Gal-(1-3)-ß-GalNAc-(1-4)-ß-Gal-(1-4)-ß-Glc-(1-1)-Cer
GD1a, IV^{3}Neu5AcII^{3}Neu5AcGg$_4$Cer	α-Neu5Ac-(2-3)-β-Gal-(1-3)-ß-GalNAc-(1-4)-(α-Neu5Ac-(2-3)-) ß-Gal-(1-3)-ß-GalNAc-(1-4)-ß-Gal-(1-4)-ß-Glc-(1-1)-Cer
GalNAc-GD1a, IV^{3}Neu5AcII^{3}Neu5AcGg$_5$Cer	ß-GalNAc-(1-4)-(α-Neu5Ac-(2-3)-)β-Gal-(1-3)-ß-GalNAc-(1-4)-(α-Neu5Ac-(2-3)-) ß-Gal-(1-3)-ß-GalNAc-(1-4)-ß-Gal-(1-4)-ß-Glc-(1-1)-Cer
GD1b, II^3(Neu5Ac)$_2$Gg$_4$Cer	β-Gal-(1-3)-ß-GalNAc-(1-4)-(α-Neu5Ac-(2-8)-α-Neu5Ac-(2-3)-) ß-Gal-(1-3)-ß-GalNAc-(1-4)-ß-Gal-(1-4)-ß-Glc-(1-1)-Cer
GD1b-lactone, II^3(Neu5Ac-(2-8,1-9)-Neu5Ac) Gg$_4$Cer	β-Gal-(1-3)-ß-GalNAc-(1-4)-(α-Neu5Ac-(2-8, 1-9)-α-Neu5Ac-(2-3)-) ß-Gal-(1-3)-ß-GalNAc-(1-4)-ß-Gal-(1-4)-ß-Glc-(1-1)-Cer
GT1b, IV^{3}Neu5AcII^3(Neu5Ac)$_2$Gg$_4$Cer	α-Neu5Ac-(2-3)-β-Gal-(1-3)-ß-GalNAc-(1-4)-(α-Neu5Ac-(2-8)-α-Neu5Ac-(2-3)-) ß-Gal-(1-3)-ß-GalNAc-(1-4)-ß-Gal-(1-4)-ß-Glc-(1-1)-Cer
O-Acetyl-GT1b, IV^{3}Neu5AcII^{3}Neu5,9Ac$_2$-(2-8)-Neu5Ac) Gg$_4$Cer	α-Neu5Ac-(2-3)-β-Gal-(1-3)-ß-GalNAc-(1-4)-(α-Neu5,9Ac$_2$-(2-8)-α-Neu5Ac-(2-3)-) ß-Gal-(1-3)-ß-GalNAc-(1-4)-ß-Gal-(1-4)-ß-Glc-(1-1)-Cer
GQ1b, IV^3(Neu5Ac)$_2$II^3(Neu5Ac)$_2$Gg$_4$Cer	α-Neu5Ac-(2-8)-α-Neu5Ac-(2-3)-ß-Gal-(1-3)-ß-GalNAc-(1-4)-(α-Neu5Ac-(2-8)-α-Neu5Ac- (2-3)-)ß-Gal-(1-3)-ß-GalNAc-(1-4)-ß-Gal-(1-4)-ß-Glc-(1-1)-Cer
O-Acetyl-GQ1b, IV^3(Neu5Ac)$_2$II^3(Neu5Ac)$_2$Gg$_4$Cer	α-Neu5Ac-(2-8)-α-Neu5Ac-(2-3)-ß-Gal-(1-3)-ß-GalNAc-(1-4)-(α-Neu5,9Ac$_2$-(2-8)-α-Neu5Ac-(2-3)-)ß-Gal-(1-3)-ß-GalNAc-(1-4)-ß-Gal-(1-4)-ß-Glc-(1-1)-Cer

neurons, and protective effects against different forms of neuronal damage (79, 80). The ability of GM1 to potentiate or replace neurotrophins in their actions (81) is at least in part dependent by its capability to tightly bind Trk (82, 83) and stimulate Trk kinase activity, receptor autophosphorylation and dimerization (84-86). A significant fraction of Trk receptor population can be usually detected in lipid rafts (87-89). Glycosylated Trk is able to form Trk-GM1 complexes, which are essential for the targeting of Trk into GM-enriched domains (90), and for GM-induced activation of the receptor (85).

In rat neurons, the activation of the lipid raft-associated ganglioside-specific sialidase Neu3 (91) is essential for axon specification and neuronal polarization (92) and anti-GM1 autoantibodies from patients affected by the axonal form of the Guillan-Barré syndrome were able to abolish NGF-induced Trk activation and to alter the association of the receptor with lipid rafts (93).

Upon activation, lipid raft-associated membrane receptors can give rise to signal propagation that involves several proteins

Table 2. Proteins involved in signal transduction associated with lipid rafts in neurons

Protein class	Proteins	References
Receptor tyrosine kinases	Trk A	(72, 73)
	Trk B	(74-76)
	c-Ret	(77)
	ErbB	(78)
	Eph	(79, 80)
GPI-anchored receptors	GFRa	(77)
G protein-coupled receptors	Cannabinoid receptors	(62, 81, 82)
	α1-, β1-, β2-adrenergic receptors	(83)
	Adenosine A1 and A2 receptor	(75, 84-87)
	GABAb receptor, serotonin	(88)
	5HT2 receptor	(89)
Glutamate receptors	AMPA, NMDA and mGluR	(90-93);
Src family non-receptor tyrosine kinases and related proteins	c-Src, Lyn, Fyn;	(32, 36, 73, 94-102)
	Cbp/PAG	(95)
Heterotrimeric and small GTP-binding proteins	Gαo, Rac1	(101, 103-106)
Cell adhesion molecules	NCAMs, TAG-1, Thy-1, F3/contactin	(98, 100, 106-109)
Postsynaptic density complex proteins	PSD-95, PSD-93	(91, 93, 110-111)

intrinsically present in the lipid membrane domain. Examples are represented by EGFR, PDGFR, p75NTR, GFRα (94-96) and the neural cell adhesion molecule TAG-1 (97). In other cases, activation of a signaling protein involves its translocation in/out from lipid rafts to non-raft membrane region or to different intracellular sites, or its partition among different raft subpopulation. For example, TrkB neurotrophin receptor can be translocated to lipid rafts from other cellular compartments upon stimulation with its ligand BDNF (88, 89), and association with lipid rafts favors the interaction of TrkB with the tyrosine kinase Fyn, that likely represents an important tuning mechanism for BDNF *in vivo* (87). Frequently, lipid raft-mediated recruitment allows the reciprocal engagement of co-receptor molecules that are not reciprocally interacting in the resting state. The neuronal adhesion receptor NCAM can be recruited into lipid rafts at the neuronal surface via lateral interactions with prion protein. NCAM association with PrP within lipid rafts creates a multimeric signaling receptor whose engagement leads to the activation of Fyn kinase and ultimately promotes neurite outgrowth (71). Glial cell line-derived neurotrophic factor (GDNF) is a family of ligands that binds specific GPI-anchored receptors usually enriched in lipid rafts, GFRαs, however GDNF transduces its signal via a common tyrosine kinase receptor, c-Ret (94). c-Ret is recruited to lipid rafts thanks to its interaction with GFRα, giving rise to a signal transduction cascade important for neuron survival and neurite outgrowth (98-100). In particular, GDNF-mediated segregation of c-Ret into lipid rafts and formation of a signaling complex with GFRα protects c-Ret from proteasome-dependent degradation, thus potentiating GDNF signaling (101). More in general, it has been suggested that the relocalization of c-Ret into different subsets of lipid rafts might represent an efficient way to segregate the different biological functions of c-Ret (102).

It is worth to note that Src family non-receptor tyrosine kinases, like c-Src, Lyn and Fyn, which play multiple and important roles relevant to the acquisition and maintenance of neuronal functions (103, 104), are usually highly enriched in lipid rafts (105) where are closely associated with gangliosides. In neuroblastoma cells, neurite outgrowth can be induced by anti-ganglioside antibodies (106) or by the administration of exogenous gangliosides, and neuritogenic concentration of gangliosides were able to induce c-Src activation

followed by mitogen-activated protein kinases activation. In granule neurons, antibody-mediated cross-linking of GD3 induced Lyn activation.

Fyn plays a relevant role in Alzheimer's disease (AD). It is known that it interacts with the adaptor protein Disabled1 (Dab1), which in turn represents a critical partner for the amyloid precursor protein (APP) (107). Fyn regulates the reciprocal interactions and the targeting to lipid rafts of APP and Dab1 (108), driving APP away from the amyloidogenic pathway, which is largely a lipid raft-dependent event.

Lipid rafts serve as signaling platforms for many events involved in the development and maintenance of the function of neurons, and of the functional interactions between neurons and glial cells. The complex molecular machinery associated with synaptic transmission is localized in lipid rafts, and its normal function is dependent on lipid raft organization. Lipid rafts play significant roles in neuronal survival, axon growth, guidance and regeneration (109), partly by modulating neurotrophic factor signaling (95), partly by modulating the interaction of neuron with astrocytes and oligodendrocytes or Schwann cells (110, 111). One example that depicts the complexity of lipid raft-mediated events in the nervous system is represented by the multifaceted role played by lipid rafts in myelin organization and stability, and in myelin-axon interactions.

GalCer and sulfatide are the major GSL in myelin. Their synthesis is maximal during myelin extension *in vivo* and in cultured oligodendrocytes (112, 113), and is essential for properly organized myelin, as revealed by studies on galactolipid-null mice (114-116). This is at least in part explained by the ability of GalCer and sulfatide to establish lateral carbohydrate-carbohydrate interactions and organize a specific type of lipid raft in myelin (111, 117) called "glycosynapse". In the myelin "glycosynapse" there are several proteins critical for myelin formation, maintenance and function (118), that actively participate to myelin-axonal communications. Lipid rafts play a relevant role with this respect also on the axon side. In fact, long-term axon-myelin stability is due to the trans-interaction between the ganglioside GD1a, (and GT1b), and the myelin-associated glycoprotein MAG (119, 120), a neural cell adhesion molecule belonging to a subgroup of the immunoglobulin superfamily, termed sialoadhesins. MAG has been identified as one of the several myelin-associated inhibitors of axonal regeneration (121-123) and it has been suggested that axonal gangliosides could be the relevant MAG receptors in MAG-dependent axon outgrowth inhibition (124, 125). However, MAG inhibition of axon outgrowth is in part linked by its ability to bind Nogo-R1 (NgR1), a GPI-anchored protein expressed in many types of neurons in CNS (126, 127), which suggests a potential role of NgR1 as a MAG receptor in axon outgrowth inhibition. Two classes of transmembrane co-receptors have been so far shown to associate with NgR1, such as p75 and TROY, both belonging to the tumor necrosis factor receptor family, and LINGO1, a functional component of the Nogo receptor signaling complex, thus originating a complex constituted by NgR1-p75/TROY-LINGO1 (123). Interestingly, NgR1, p75 and LINGO are enriched with polysialogangliosides in neuronal lipid rafts (124, 128), and it has been proposed that axonal ganglioside-rich rafts could be essential for the stable association of the different components of the MAG receptor (129).

4. LIPID RAFTS AND DISEASES OF THE NERVOUS SYSTEM

The lateral interactions between components must be modulated, both in time and in space (1, 130) to explain that rafts are responsible for neuronal functions. A membrane-associated protein can partition between lipid raft and non-lipid raft regions, it can be distributed among different subpopulations of lipid rafts that are dynamically interacting, and in some cases fusing together forming higher scale signaling platforms. It is not surprising that changes in lipid composition can deeply affect lipid raft dynamics, organization and thus functions. Regulation of lipid raft organization by changes in lipid composition does probably represent a phenomenon of physiological importance. Complex lipid composition of the nervous system is developmentally regulated and complex lipid homeostasis is carefully maintained by a series of metabolic pathways. The ability to generate lipid mediators by the hydrolysis of membrane-associated GPL is known from a long time (131).

The presence of both a sialidase (132, 133), and a sialyl transferase (134) activity at the surface of synaptosomal membranes, rich of a gangliosides, suggests that the local glycosphingolipid composition of the neuronal plasma membrane in specialized membrane areas could be

modulated by a sialylation-desialylation cycle. Today it is getting clear that a subset of several different glycosylhydrolases (sialidase (16, 92), β-hexosaminidase (135), β-galactosidase (136, 137), β-glucosidase (136, 137)) and glycosyltransferases (sialyl transferase (138, 139), β-galactosaminyl transferase (138)) are present and active in specialized areas of plasma membranes in many cell types, including neurons and neural stem cells (140), allowing the sequential removal/addition of sugar residues from/to the oligosaccharide head groups of membrane glycolipids. Considering the importance of the glycan chain of glycosphingolipids in the lateral interactions that drive the formation of lipid rafts, and that allows the interaction with raft-associated proteins, the local metabolism of lipid-bound saccharide chains probably represents an efficient mechanism to modulate the organization and function of lipid rafts as signaling platforms (141). Sphingomyelin in plasma membrane lipid rafts can be as well hydrolyzed with the formation of ceramide by the activity of different sphingomyelinases (142, 143), and conversely plasma membrane ceramide can be converted to sphingomyelin by the action of a specific plasma membrane-associated sphingomyelin synthase (SMS2) (144). Ceramide at the plasma membrane can be as well generated by the sequential removal of sugar units from a ganglioside oligosaccharide chain (145). It has been suggested that the generation of ceramide from plasma membrane sphingolipids (142, 146) is followed by a dramatic change of the lipid aggregation properties. This is responsible for massive rearrangements of lipid raft organization and for the fusion of small scale pre-existing rafts into large ceramide-rich signaling platforms (147), this being coupled with changes in the membrane curvature, eventually participating in inward or outward vesiculation. Cholesterol rapidly undergoes flip-flop with redistribution between the two leaflets (148), and to lateral redistribution into and out from lipid rafts (149). Moreover, even if GPL are less enriched in lipid rafts than in non raft-membranes, they still represent the major lipid family in lipid rafts, thus alterations in the fatty acid composition of GPL (and in particular enrichment in molecular species containing high levels of polyunsaturated fatty acids) might contribute as well to physiologically relevant changes in lateral organization of lipid rafts (150). Finally, lipid raft organization can possibly be deeply modulated by other lipids that are usually not regarded as classical raft-forming lipids, such as cholesterol oxidation products (151) and endocannabinoids (152).

Alterations in lipid metabolism associated with nervous system dysfunctions might lead to abnormal lipid raft functions, and contribute to pathogenesis of nervous system diseases. Inherited metabolic diseases due to inborn errors of complex lipid metabolism, such as sphingolipidosis, due to defects in one of the the lysosomal glycohydrolases (153, 154) or sphingomyelinase (155), are progressive and usually fatal neurodegenerative diseases, and it has been suggested that the accumulation of non-degraded sphingolipids might have consequences on the plasma membrane complex lipid composition (156). Similarly, some inborn errors of cholesterol turnover and storage are underlying chronic neurodegenerative disorders, and are linked to lipid raft organization, even if the underlying gene defect seems to be related to events very far from the plasma membrane. Niemann Pick type C disease is caused by mutations in the genes encoding for two cholesterol binding proteins, NPC1 and NPC2, implicated in the intracellular traffic of cholesterol, with consequent accumulation of cholesterol and other lipids in the late endosome/lysosome compartment. Altered composition and organization of lipid rafts has been hypothesized to play a significant role in the etiology of this disease (157). ApoE genotype represents the major genetic risk for the development of Alzheimer's disease (AD). In particular, inheritance of the E4 isoform of apoE highly increases the risk of developing AD, while other isoforms might represent a protective factor against the disease (158). ApoE, produced by glial cells and secreted in the form of lipoprotein like particles, is the most abundant apoprotein in CNS where it is likely involved in cholesterol homeostasis (159). In particular, it has been suggested ApoE-mediated delivery of cholesterol to neurons and oligodendrocytes might be involved in axonal growth and synaptic maintenance, in growth and regeneration of axons after a nerve injury, and in myelination, and in all of these events lipid rafts have been implied as possible sorting platform in lipid traffic (160, 161).

However, alterations in the metabolism of complex lipids have been reported for several important nervous system diseases, including most of the neurodegenerative diseases and the major forms of dementing disease, even in the absence of genetic links with sphingolipid and cholesterol traffic and metabolism (15, 160).

Huntington's disease, caused by polyglutamine expansion in the N-terminal portion of huntingtin protein, is associated with changes

in cholesterol metabolism, mediated by effects of mutated huntingtin on sterol regulatory element binding proteins, leading to alterations of cholesterol levels in neuronal plasma membranes negatively influencing neuronal survival (162, 163). On the other hand, a marked reduction in the ganglioside concentration was detected in the striatum of HD human brains (164), and abnormal expression of the genes encoding several glycosyltransferases involved in ganglioside biosynthesis has been reported in the striatum of a Huntington's disease mouse model and in post-mortem caudate from human HD patients (165). Consequent altered lipid raft organization might concur to the observed accumulation of mutant huntingtin in lipid rafts, that has been associated with neuronal apoptosis in a pre-symptomatic HD mouse model (166).

In Parkinson's disease patients, cholesterol serum levels are altered (167) and cholesterol balance in brain is deregulated (168), even if a causal connection with nigrostriatal neurodegeneration has not been clearly established (158). On the other hand, a strong connection has been suggested between Gaucher disease and PD (154). Moreover, several proteins whose mutations are causally connected with PD, including parkin, PINK1, α-synuclein and DJ-1 have been detected in lipid rafts in brain, neurons and astrocytes (169, 170). α-Synuclein interacts with gangliosides and cholesterol, and the association with these lipids affects the tridimensional structure of the protein and its intracellular traffic (171). Furthermore, multiple and severe alterations in the lipid composition such as elevated ratio between saturated and polyunsaturated fatty acids in complex lipids, and strong reduction in cerebrosides and sulfatides, have been observed in lipid rafts purified from the frontal cortex of PD patients (172).

Alzheimer's disease is probably the neurodegenerative disease where a possible causative role of alterations in cholesterol metabolism has been most intensely debated. Beside the clear correlation of the genetic risk of developing AD with mutations of apoE, opposite findings have been reported on the levels of cholesterol, on cholesterol precursors and metabolic enzymes in the brain of AD patients, and several studies have explored a possible correlation between circulating lipid levels or lipid lowering treatments and AD risk with controversial and non-conclusive results (173, 174). Very complicated is the scenario also for AD-related alterations in sphingolipid metabolism and composition. Lipidomic analysis on post-mortem brains of subjects with pre-clinical or early stage AD revealed reduced sulfatide and sphingomyelin, and increased ceramide content (175)). Deregulated brain ganglioside metabolism has been reported in brains of AD patients and in transgenic mice models of the disease (176). The patterns of ganglioside alterations in AD are very complex and differ according to age of onset and type of mutation, suggesting that different GSL-regulated events contribute to the onset of different AD forms. Low ganglioside content and altered ratio between a-series and b-series structures, and elevated levels of simpler gangliosides, that usually are minor component of the brain ganglioside mixture, have been observed in several brain regions of AD and dementia of the Alzheimer type (DAT) patients (177-179) with respect to age-matched healthy controls. Moreover, multiple changes in the gene expression of several enzymes that control SL metabolism (including down regulation of several glycosyltransferases, consistently with the reported reduction of ganglioside levels, and upregulation of enzymes involved in the de novo ceramide synthesis) were observed in dementia and AD patient brains (180). On the other hand, lipid rafts from the frontal and temporal cortices of AD patients contain a higher concentration of gangliosides GM1 and GM2 respect to age-matched control brains (181).

Lipid rafts with altered lipid composition could result in the defective functions of raft-associated proteins, and the consequent abnormal signaling could contribute to the onset of the disease. On the other hand, a common trait of several neurodegenerative disease is represented by the misfolding of a cellular protein, with the consequent loss of normal function of the protein and/or formation of a toxic form, that in the nervous tissue gives rise to the formation of poorly soluble fibrils or particles. α-Synuclein in PD, amyloid β peptide (Aβ) in AD and the scrapie prion protein, PrP^{Sc}, in transmissible encephalopaties are the most notable examples. The mechanisms by which the amyloidogenic proteins exert their detrimental effects on the nervous system are not fully understood, and probably multiple and multifaceted (182, 183), and their actual weight in determining the onset and the evolution of the disease is still sometimes controversial (184). The mechanisms leading to the formation of the amyloidogenic, pathological forms of these proteins are different for the different proteins, however lipid rafts seem to play a relevant role in these events. In other words, lipid rafts with altered lipid composition

might facilitate the formation of the pathological forms of these proteins. In some cases, a non physiological binding of the protein to the membrane, and the conversion into the pathological form are dependent on the membrane lateral order, in other cases they are modulated by a direct interaction with membrane lipid molecules. α-synuclein association with model membranes increased with membrane curvature (which is strongly connected with the lateral segregation of membrane lipids such as gangliosides) and rigidity, was negatively affected by the presence of cholesterol and was lost upon thermal transition to the liquid disordered phase, indicating that membrane order, as a collective property of the membrane microenvironment, rather than specific lipid-protein interactions is relevant in this case (185). Conversely, association of α-synuclein with a cholesterol-enriched ternary membrane system putatively mimicking lipid rafts, perturbed the lipid packing within the membrane l*o* phase (186). The structure of α-synuclein contains two distinct cholesterol binding domains (with high and low different affinity for the ligand, respectively), and a glycosphingolipid-binding domain. Aβ as well can directly bind cholesterol and GM1 ganglioside (interacting with the ganglioside oligosaccharide chains by sugar-specific interactions) (187, 188). Association of a certain protein with lipid rafts or with lipid raft cholesterol and gangliosides is underlying a very complex network of molecular interaction. For example, interaction with cholesterol can directly affect protein conformation, or indirectly, by modulating sphingolipid-protein interactions (189). On the other hand, lipid-mediated interactions are not the unique players in this scenario. Amyloid precursor protein (APP) directly interact with cholesterol (190), but its targeting to lipid rafts is controlled by the activity of the tyrosine Fyn kinase, that phosphorylates one of the interacting partners of APP, the adaptor protein Disabled1 (108).

APP is a transmembrane protein whose physiological functions are still enigmatic (191). It seems to be involved in the transduction across the membrane of signals relevant to neuronal adhesion, survival and synaptic functions (192). Association of APP with lipid rafts bearing anomalous lipid composition could alter the functions of APP as a signaling molecule, possibly altering its signaling through $G_{\alpha o}$ (193). On the other hand, great emphasis in AD pathogenesis has been given to overproduction of Aβ peptides (that accumulate in the brain lesions that are commonly thought to cause AD (194)). Lipid rafts contain not only APP, but also APP-derived proteolytic fragments, including Aβ and the proteolytic enzymes involved in APP amyloidogenic processing. In particular they are enriched in active β and γ-secretases, and the production of Aβ amyloid is preferentially, even if not exclusively localized within lipid rafts. In other words association with lipid rafts is a pre-requisite for the amyloidogenic processing of APP, that could be favored by altered lipid raft organization driven by changes in their lipid composition. Conversely, cleavage of APP also has a direct influence on the cellular lipid composition, because APP processing alters the synthesis rate of several lipids enriched in lipid rafts (195). Moreover, γ-cleavage of APP, also taking place in lipid rafts, leads to the release of the APP intracellular C-terminus domain (AICD), an APP metabolite which has distinct physiological functions, being able to regulate the expression of several genes. Remarkably, AICD released from APP can participate in the regulation lipid metabolism (plasmalogen synthesis by controlling the expression of alkyl dihydroxyacetonephosphate synthase, sphingolipid synthesis by controlling the expression of serine-palmitoyltransferase (196)), thus affecting lipid raft composition. On the other hand, targeting of APP to lipid rafts is regulated via Src family kinase Fyn and Dab1. After soluble Aβ is formed, the next step toward the toxic effect underlying AD is its conversion into aggregated forms that are the pre-requisite for the formation of insoluble amyloid fibrils. Binding of Aβ with membrane gangliosides within lipid rafts (197, 198), drives its conformational transition by favoring the conversion of the aggregated form (199) leading to Aβ fibrillogenesis (200). On the other hand, interaction of GM1 with Aβ can lead to the formation of toxic soluble oligomers, that exert their detrimental effects through the high affinity binding with another protein enriched in lipid rafts, cellular PrP (201).

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