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Review

Lipid rafts: Keys to neurodegeneration

Cara-Lynne Schengrund*

Department of Biochemistry and Molecular Biology, The Pennsylvania State University College of Medicine, Hershey, PA 17033, United States

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ABSTRACT

The increase in life expectancy seen in many countries has been accompanied by an increase in the number of people living with dementia and a growing need for health care. The large number of affected individuals emphasizes the need to identify causes for the phenotypes associated with diseases such as Alzheimer's, Parkinson's, amyotrophic lateral sclerosis, Huntington's, and those caused by prions. This review addresses the hypothesis that changes in lipid rafts induced by alterations in their ganglioside and/or cholesterol content or the interaction of mutant proteins with them provide the keys to understanding the onset of neurodegeneration that can lead to dementia. The biological function(s) of raft-associated gangliosides and cholesterol are discussed prior to reviewing what is known about their roles in lipid rafts in the aforementioned diseases. It concludes with some questions that need to be addressed in order to provide investigators with the basis for identifying small molecule agonists or antagonists to test as potential therapeutics.

Contents

1. Introduction

The need for understanding the underlying causes that lead to neurodegeneration or disruption of neural transmission and dementia has significant clinical importance. In a statistical analysis of dementia [29], it was estimated that 4.6 million people aged 60 and over develop dementia annually and it was predicted that the number will double every 20 years. When considered in terms of years lived with disabilities by those over 60, dementia is responsible for more disability than stroke, musculoskeletal disorders, cardiovascular disease and all forms of cancer. In the United States more than 4 million people have AD and it is thought that about half of those aged 85 and over are affected [29]. AD is the fifth leading cause of death of those over 65 and seventh overall. Approximately 1 in 100 people over 60 will develop Parkinson's Disease, and about 1/3 of those affected will show signs of dementia in the final stages. With the population of people aged 65 and over expected to rise from the ~12% that it was in 2006, to ~20% in 2030, it is clear that if nothing is done, these problems will continue to grow placing even more of a burden on the health care system. AD

* Tel.: +1 717 531 8048; fax: +1 717 531 7072.
E-mail address: cxs8@psu.edu.

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Table 1
Composition of the carbohydrate portion of glycosphingolipids discussed in this review.

Ganglioside	Saccharide composition
GM3	NeuAcα2–3Galβ1–4Glcβ1–[a]
GD3	NeuAcα2–8NeuAcα2–3 Galβ1–4Glcβ1–
GM2	GalNAcβ1–4(NeuAcα2–3)Galβ1–4Glcβ1–
GD2	GalNAcβ1–4(NeuAcα2–8NeuAcα2–3)Galβ1–4Glcβ1–
GM1 (LIGA20-GM1[b])	Galβ1–3GalNAcβl–4(NeuAcα2–3)Galβ1–4Glcβ1–
GM1b	NeuAcα2–3Galβ1–3GalNAcβ1–4Galβ1–4Glcβ1–
Fuc(Gal)-GM1	Galαl–3(Fucαl–2)Galβ1–3GalNAcβ1–4(NeuAcα2–3)Galβ1–4Glcβ1–
GD1a	Neu Acα2–3Galβ1–3GalNAcβ1–4(Neu Acα2–3)Galβ1–4Glcβ1–
GD1b	Galβ 1–3GalNAcβ1–4(Neu Acα2–8Neu Acα2–3)Galβ 1–4Glcβ1–
GT1b	Neu Acα2–3Galβ1–3GalNAcβ1–4(Neu Acα2–8Neu Acα2–3)Galβ1–4Glcβ1–
GQ1b	NeuAcα2–8NeuAcα2–3Galβ1–3GalNAcβ1–4(NeuAcα2–8NeuAcα2–3)Galβ1–4Glcβ1–

[a] Glcβl- of each oligosaccharide shown is linked to ceramide.
[b] LIGA20 differs from GM1 in that it has a dichloroacetyl group instead of afatty acid at the 2-amino position of sphingosine [77].

and Parkinson's are not the only disorders affecting neuronal function. Amyotrophic lateral sclerosis (ALS), Huntington's and prion diseases, while not as prevalent, also contribute to the health care burden associated with dementia.

Alterations in lipid rafts have been hypothesized to contribute to the loss of neural function and potentially to the cell death associated with each of the diseases mentioned, e.g. [37,68,88,90,162]. Recognizing that there are skeptics when it comes to lipid rafts, it is difficult for anyone to argue with the possibility that there are areas on the membrane in which proteins involved in signal transduction, sphingolipids, including glycosphingolipids (GSLs) such as gangliosides that can modulate signal transduction, and cholesterol, the glue that holds things together, may be enriched (Fig. 1). Interestingly, while the existence of lipid rafts may be questioned, that of caveolae, a recognized subset of lipid rafts characterized by the presence of caveolin-1 and the resultant formation of an indented area on the membrane [125], is not. Despite questions regarding the existence of lipid rafts, it has been shown that alteration of the ganglioside and/or cholesterol composition of the plasma membrane can affect signal transduction, e.g. [131]. While the ganglioside composition has been shown to vary in different areas of the brain [64], it is recognized that within specific cells the composition of lipid rafts is not fixed but dynamic, with molecules able to move into and out of them. An example of this mobility can be seen in a recently published study in which fluorescence resonance energy transfer was used to monitor Akt signaling dynamics in microdomains [34]. Despite the fluidity, studies indicate that specific gangliosides found within a cell may not cocluster in the same lipid rafts [148].

While the need for gangliosides for normal development was well known from studies of animal mutants, e.g. [2,60], the question of what effect failure to synthesize GM3 would have on humans was not answered until the report of identification of a loss-of-function inborn mutation in GM3 synthase [127]. The mutation resulted in failure to synthesize GM3 from CMP-sialic acid and lactosyl ceramide, resulting in developmental stagnation, regression, and death of the affected children. Failure to synthesize GM3 results in loss of expression of the more complex gangliosides found in brain and for which it serves as a precursor (e.g. GM1, GD1a, GD1b, and GT1b, ganglioside nomenclature is that proposed by [137]. The carbohydrate structures of glycolipids discussed are shown in Table 1. For a review discussing ganglioside metabolism see Huwiler et al. [52].

The underlying hypothesis for this review is that changes in lipid rafts induced by changes in ganglioside and/or cholesterol content or the interaction of mutant proteins with them, results in development of specific types of dementia. While studies of the effects of altered lipid composition on cell behavior have been carried out over a number of years, it is only since the emergence of the concept of detergent resistant membrane domains [17] or lipid rafts [125] that the hypothesis that changes in the lipid composition of rafts might be an underlying cause of dementia has begun to emerge. In fact research published in the 1990s indicated that changes in expression of GM1, now known to be associated with lipid rafts [148], might be causative, e.g. [33,159]. Gangliosides, with an emphasis on GM1, GD1a, GD1b, and GT1b which account for 65–85% of the ganglioside content in brain, were specifically selected for consideration because of their high concentration in the brain [109] and specifically in gray matter that has four to five-fold more ganglioside content per mg of protein than white matter [64]. Cholesterol is of interest because accumulating evidence indicates that alterations in its concentration may contribute to dementia. This led to the recent statement that methods to adjust cholesterol metabolism in the brain need to be developed in order to target cholesterol-dependent damage to neurons [59]. This review will briefly discuss studies done to define the biological role(s) of gangliosides, and evidence for the need for cholesterol prior to reviewing what is known about the roles of lipid rafts in several diseases known to cause dementia. It will conclude with suggestions of areas for future study.

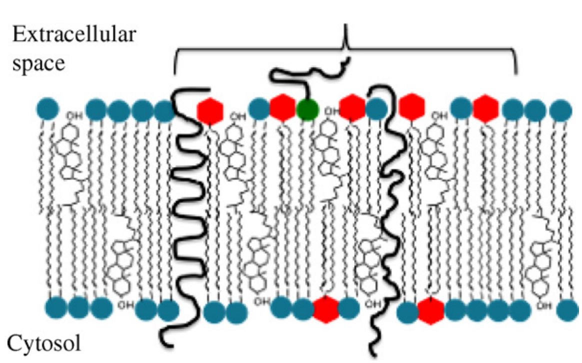

Fig. 1. Schematic of a lipid raft. ● indicates phospholipids, ⬢ sphingolipids, black curvey lines proteins, and ● a GPI linkage. The bracket indicates the portion of the membrane comprising the raft.

2. Gangliosides affect cell behavior

Changes in ganglioside composition can alter cell behavior. Some early examples include *in vivo* observations indicating that accumulation of the ganglioside GM2 in Tay-Sachs disease and GM1 in GM1-gangliosidosis resulted in expression of meganeurites by some neurons ([106,105], respectively). They were also shown to help regulate granule-cell migration [55]. These observations led to numerous studies of the effects of added gangliosides on neural cells in culture. These studies were based on the fact

Table 2
Examples of the effects of specific glycosphingolipids on selected proteins.

Glycosphingolipid	Effect	Reference
Mixed brain gangliosides	↑ Adenylate cyclase activity	[97]
GTlb > GDla = GDlb > GM3 = GMl	↓ Protein kinase C	[65]
GM1, GD1a, GT1b	↓ cAMP kinase	[161]
GT1b > GD1a > GM1	↑ Calmodulin-dependent cyclic nucleotide phosphodiesterase	[161]
de-N-acetyl-GM3	↑ EGFR autophosphorylation	[43]
GM3, GD1a, GT1b	↓ EGFR autophosphorylation	[85]
GM1	↑ TrkA	[107]
LIGA20 (modified GM1)	↑ TrkB	[7]
GM1, GM2, GD1a, GD3, GT1b	↓ PDGFR dimerization	[145]
Over expression of GM1	↓ TrkA phosphorylation	[95]
Cross-linked GM1	↑ Ca^{2+} influx	[154]
Cross-linked Fuc(Gal)GM1	↑ SFKs Fyn and Yes	[158]
GM1, GM2	↓ Insulin stimulation of the insulin receptor	[115]
GM1	↑ MAPK and CREB	[21]

that exogenous gangliosides can be taken up by cells and incorporated into their plasma membranes. Evidence for this was provided by the observation that when cells lacking GM1, hence not susceptible to the action of cholera toxin, were grown in medium containing GM1 they became susceptible to the toxin [91]. In order for the cells to become susceptible they had to incorporate the GM1 in such a way that the carbohydrate portion was exposed on the outer surface of the plasma membrane as that is the portion bound by the toxin's binding subunit (CTxB [117]). Observations from examples of *in vitro* studies in which GM1 was either added or its location/expression altered include: addition of GM1 to Neuro-2a murine neuroblastoma cells induced neurite formation [24] and enhanced their cytoskeletal organization [132]. Studies with rat cerebral astroglial cells indicated that cross-linking of cell surface GM1 with CTxB induced a marked change in their morphology [25]. Use of filipin to sequester cholesterol and disrupt lipid rafts enhanced both GM1 expression on the nuclear membrane and axonogenesis by N2a cells [100].

In order to use gangliosides to treat disorders in the central nervous system it was necessary to know whether those administered by other than injection directly into an area of the central nervous system were actually taken up by the brain. The answer to that question was that iv, im, or sc injection of mice with ^{3}H-labeled gangliosides resulted in recovery of a small amount (<1.5%) from their brains a few hours after injection [142]. This observation indicated that exogenous gangliosides could reach the CNS and interact with cells to induce changes in their behavior. Subsequent studies indicated that the LIGA20 derivative of GM1, GM1 with the fatty acid replaced with dichloroacetone, could cross cell membranes more readily than GM1 [155]. These observations provided the rationale for a number of studies of the effects of exogenous gangliosides on *in vivo* regenerative or behavioral responses in animals that had been lesioned in a specific site. For example, MPTP is known to destroy neurons in the substantia nigra. Treatment of monkeys with GM1 after exposure to MPTP protected them from its deleterious effects [118]. For a review of earlier studies see Schengrund [116].

2.1. Clinical trials to determine efficacy of GM1 for treatment of CNS problems

The positive results seen in animals led to studies of the efficacy of exogenous gangliosides for enhancement of recovery from spinal cord injuries, and the treatment of Alzheimer's and Parkinson's diseases (AD and PD, respectively). A preliminary study of the effect of GM1 on spinal cord injury indicated that iv administration of 100 mg of GM1 per day for 18–32 days appeared to enhance recovery of neurologic function. However, those results were published with the caveat that a larger study was necessary [36]. Results of a subsequent, much larger study (760 patients) did not show a significant benefit in the primary efficacy analysis of the trial. The researchers did note that the GM1 appeared to have a greater beneficial effect on the less severely injured patients [35]. However, subsequent analysis of the data led to the conclusion that GM1 had not reduced the death rate in spinal cord injury patients and did not improve recovery or quality of life for the survivors [20]. When looking at the effects of GM1 on spinal cord injury care must be taken to consider the amount of methylprednisolone used to reduce inflammation. In studies of spinal cord injuries in mice, GM1 was found to block the effects of methylprednisolone by presumably inhibiting its anti-inflammatory effects [22].

Support for the idea that disruption of the lipid environment may underlie the problems seen in both Parkinson's (PD) and Alzheimer's disease (AD) is provided by the positive results obtained in clinical trials to test the ability of GM1 to ameliorate associated symptoms. The study of the effectiveness of GM1 for treating PD followed up on an open study of the effect of GM1 given to 10 people with PD. The results of that study indicated that most patients given an initial bolus of GM1 iv followed by 200 mg of GM1 per day via 2 sc injections (100 mg each) for 18 weeks showed some improvement between 4 and 8 wks and that those improvements lasted for the duration of the study [119]. The randomized placebo-controlled study that followed, enrolled 48 people having mild to moderate PD with 45 of them completing the 16-wk study. Those in the treated group were given GM1 in the same manner as those in the open trial and controls were given placebo in the same manner. The results indicated that after just 4 wks, GM1-treated patients did significantly ($\rho = 0.0002$) better on the Unified Parkinson's Disease Rating Scale (UPDRS), used as the primary efficacy measure, than placebo treated individuals and that continued over the 16 wk time period. The results also showed no severe adverse effects due to administered GM1. At the end of the 16 wk trial, patients were given the opportunity to continue to take GM1 in an open extension of the study. Twenty-one elected to do so and were followed for at least a year. At the end of the year 18 of them had better UPDRS motor scores than measured for the original base line at the start of the double-blind study. Again, no clinically significant changes were seen in blood chemistry or hematology measurements [120]. Based on these observations it is curious that no multi-year follow-up information on these individuals has been made available and that additional clinical trials have either not been done or the results have yet to be published.

The sole clinical trial done to test efficacy of exposure to exogenous GM1 on AD included five individuals with early-onset AD. GM1 was administered to each by continuous injection into the frontal horns of the lateral ventricles for a year. Twenty-30 mg of

GM1 per day was found to be optimal. Testing of the individuals at 1, 3, 6, 9, and 12 months indicated that by 3 months they had become more active and at the end of the study, all five patients indicated that they felt better and their relatives also thought they had improved [6,138].

2.2. Possible mechanisms by which gangliosides affect cell behavior

In addition to looking at morphological and physical changes induced by exogenous gangliosides, investigations have been carried out to determine potential mechanism(s) of action. Examples of the effects of specific gangliosides on selected proteins are shown in Table 2. Perhaps best understood is their ability to modulate the effects of binding of growth factors to their receptors. In 1982, Bremer and Hakomori [16] reported that the ganglioside GM3 appeared to inhibit function of the epidermal growth factor receptor (EGFR). Since then numerous reports have appeared indicating that gangliosides affect not only EGFR but receptors for platelet-derived growth factor (PDGFR), fibroblast growth factor (FGFR), nerve growth factor (NGF), and insulin e.g. ([145,113,93,139], respectively). EGFR, PDGFR, FGFR, and insulin receptors are tyrosine kinase receptors which when bound by the appropriate ligand undergo autophosphorylation initiating signal transduction. It has been postulated that gangliosides can affect these interactions by interacting with the factor and presenting it to its receptor or by interacting with the receptor thereby affecting its ability to bind the factor [83]. Depending upon the ganglioside–protein interaction within rafts, the response may be either inhibited or enhanced. For example, GM3 inhibits EGFR autophosphorylation [84] while GD3 and GT1b enhance it [74]. Another example of opposing effect, is the enhancement of axonal growth by GM1b and its inhibition by GD1a and GT1b. GM1 interacts strongly with neurotrophic tyrosine kinase A (TrkA), remaining associated with the TrkA during SDS-PAGE [93]. This interaction enhances binding of NGF to TrkA and initiates a signal cascade that results in axonal growth [1]. Cells lacking GM1 do not express cell surface TrkA and as a result it is not autophosphorylated in response to added NGF [92]. In contrast to the positive effect of the interaction of GM1 with TrkA on NGF-induced axonal growth, when either GD1a or GT1b interacts with the neurotrophin receptor $p75^{NTR}$ the complex is held in a lipid raft where it modulates the effects of other proteins such as Trk, and inhibits axon growth [1].

That sialic acid containing molecules function in expression of axons was seen when transfection of neuroblastoma cells with plasma membrane-associated sialidase 3 was found to enhance formation of neurites with axonal properties [103]. Interestingly, sialidase 3 was observed to enhance axonogenesis by catalyzing the cleavage of sialosyl residues from GD1a and/or GT1b, thereby eliminating inhibition of axonogenesis, while the GM1 produced enhanced it [86]. The observations described above indicate that the distribution of gangliosides within lipid rafts can significantly affect signal transduction and resultant cell behavior. Alteration of the distribution of gangliosides within lipid rafts can also induce cellular changes. When GM1 residues were cross-linked using either CTxB [154] or galectin-1 (a homodimeric galactose-binding protein, [149]) it affected both Ca^{2+} influx and neurite outgrowth. Wu et al. [154] found that GM1 in NG108-15 cells was associated with the α5β1 integrin and when this complex was cross-linked it initiated a signal cascade that resulted in opening transient receptor potential channels that mediate the influx of Ca^{2+} and neurite outgrowth.

Interestingly, addition of GM1 to rat hepatic F258 epithelial cells protected them from benzo[a]pyrene (B[a]P)-induced apoptosis by inhibiting mitochondria-dependent acidification related to apoptosis as well as by interfering with ^{55}Fe uptake by cells [39]. Similar experiments carried out by the same lab indicated that added cholesterol also protected the cells from B[a]P-induced apoptosis in the same manner [40]. Their observations strongly support the hypothesis that B[a]P-induced changes in membrane fluidity, or more specifically in the composition of lipid rafts, initiated its toxic effects. These observations lead to the question of how changes in lipid raft cholesterol might affect cell behavior.

3. Effects of acute disruption of lipid rafts on neuroblastoma cells

In studies of the effect of acute disruption of lipid rafts by treating cells with either methyl-β-cyclodextrin (MβCD extracts cholesterol from plasma membranes [94]) or filipin (sequesters cholesterol in ultrastructural aggregates [62]) GM1 concentration was found to be significantly greater in cells in which rafts were disrupted for 12 h than in controls. GM1 associated with the nuclear membrane was also significantly increased in filipin treated cells relative to controls [100]. In addition to noting changes in both the concentration and subcellular distribution of GM1, a significant increase in axonogenesis was observed during the time the rafts remained disrupted. Similar changes were observed when MβCD was used to disrupt lipid rafts. When cells were grown under conditions that permitted resynthesis of lipid rafts, the changes were reversed. The observations seen upon disruption of lipid rafts agree with those of Wu et al. [152,153] who found that compounds such as KCl and ionomycin that caused a significant increase in GM1 and GD1a also induced axonal growth. In contrast, they found that exposure of neuroblastoma cells to compounds that upregulated expression of GM2 on the plasma membrane (retinoic acid or dibutyryl cyclic AMP) induced dendritic outgrowth. In addition to changes in ganglioside, acute disruption of lipid rafts using a low concentration of MβCD resulted in enhanced endo- and exocytosis, while disruption of lipid rafts with a four-fold greater concentration completely inhibited it [Petro and Schengrund, unpublished observation]. These observations support the hypothesis that changes in lipid raft cholesterol content that occur over time could be accompanied by a corresponding cellular response in ganglioside synthesis. These small changes could induce subtle changes that over a prolonged period could result in altered endo- and exocytosis and contribute to the overall changes seen in cell function and in the CNS, changes that could lead to dementia.

4. Cholesterol in the CNS

While exogenous gangliosides can cross the blood brain barrier to a limited extent, cholesterol cannot be readily transported across it by low density lipoproteins (lipoproteins that carry the bulk of cholesterol to cells). As a result, the brain is responsible for the synthesis and transport of cholesterol from one cell type to another. The fact that the brain consists of ∼2% cholesterol that comes from primarily *de novo* synthesis [164] means that factors affecting it could have significant effects on CNS function. Astrocytes provide cholesterol needed by the central nervous system. For a recent review on the function of sterol regulatory element binding proteins in cholesterol (and fatty acid) metabolism by astrocytes in the CNS see Camargo et al. [18]. It has been shown that astrocytes are also the major apolipoprotein E producing cells in the CNS [15] and that the cholesterol and apoE produced are released as a complex that is taken up by neurons via receptor-mediated endocytosis [47]. It is astrocyte-secreted apoE-cholesterol-containing lipoproteins that promote synaptogenesis by cultured neurons [82]. Thiele et al. [143] using a photoactivatable derivative of cholesterol showed that it was bound by synaptophysin in PC12 cells and on brain synaptic vesicles. When cholesterol was limited, formation of synaptic like microvesicles from the plasma membrane was inhibited. Use of compactin to inhibit cholesterol synthesis (inhibits 3-hydroxy-3-methyl-glutarylCoA reductase) by hippocampal slices was found to reduce synaptic plasticity [81]. This observation emphasizes the fact that one of the major roles of cholesterol is to modulate membrane plasticity and that it can have either a positive or negative effect depending upon membrane constituents. Its presence in enriched amounts in lipid rafts contributes to the predicted reduction in lateral mobility for raft components.

Oligonucleotide arrays indicated that addition of glial conditioned medium and cholesterol to cultured rat retinal ganglion cells altered expression of genes affecting development of dendrites and synapses as well as the regulation of cholesterol and fatty acid metabolism [38]. More specifically expression of 18 genes was upregulated including that for sialidase 3, a plasma membrane enzyme found in association with lipid rafts [56]. These observations indicate that cholesterol is essential for normal neuronal development and that changes in cholesterol may affect cell surface ganglioside expression by altering expression of genes involved in their metabolism such as sialidase 3. As discussed previously gangliosides can have a marked effect on the activity of various proteins involved in signal transduction while cholesterol levels can affect neuronal differentiation, membrane fluidity, and as discussed above endo- and exocytosis. While all of the foregoing supports the *hypothesis that gradual changes in the composition of lipid rafts that occur as a person ages, could reach a threshold beyond which they are expressed phenotypically*, additional support for this concept is provided by changes seen in the various dementing diseases discussed in the following.

5. Lipid rafts in dementing diseases

5.1. Alzheimer's

Although it has been over 100 years since characteristics associated with Alzheimer disease were first described, much is unknown about the sequence of changes that result in the AD phenotype. While the peptide amyloid–β42 (Aβ), produced by cleavage of amyloid precursor protein (APP) is thought to initiate cases of AD [45], errors in the cytoskeletal protein tau also contribute to neurodegeneration and dementia [44]. In addition to identifying the contributions of Aβ and tau to neurodegeneration and dementia, apoprotein E4 (apoE4) was first suggested to be a genetic risk factor for AD in 1993 [134]. It is also associated with earlier onset (see [76], for a review). The normal role of apoE is to redistribute lipids among cells [75]. Interestingly, mice expressing human apoE4 were found to have more cholesterol in the exofacial leaflet of synaptic plasma membranes than those from mice expressing apoE3 even though the total amount of cholesterol was similar [48]. Mice expressing human apoE4 were also found to have alterations in their lipid raft protein (alkaline phosphatase and flotillin-1) and lipid composition (sphingomyelin) relative to those expressing human apoE3 [53]. Interestingly, when cultured neurons were grown either in the presence of a 3-hydroxy-3-methyl-glutarylCoA reductase inhibitor such as atorvastatin, or treated with methyl-β-cyclodextrin to extract membrane-associated cholesterol, they had a lower rate of accumulation of β-amyloid than control cells [126]. An explanation for this observation may be the fact that BACE1, the β-site APP cleaving enzyme that cleaves APP at the N-terminal position of Aβ, localizes to cholesterol-rich rafts [110] and elevated levels of cholesterol enhance its activity [57] as well as that of γ-secretase (catalyzes release of Aβ) also found in lipid rafts [41]. These observations coupled with the finding that β-secretase is found in both raft and non-raft membrane regions [110] depending on cholesterol content, provide a rationale for using statins to lower cholesterol thereby reducing BACE1 activity. A reduction in BACE1 activity might be accompanied by an increase in α-secretase activity producing APPsα that is non-amyloidogenic and would be accompanied by a decrease in Aβ formation [80].

The apparent increased susceptibility to AD seen in people expressing the apoE4 allele and the changes in lipid raft composition it induces in the plasma membrane support the hypothesis that changes in the lipid composition of rafts contribute to AD pathology. Further support for this hypothesis is provided by the observation that gangliosides, known to be associated with lipid rafts, can induce the assembly of amyloid-β proteins [156,157]. Support for this is provided by the finding that inhibition of glycosphingolipid synthesis reduced secretion of Aβs [140]. Interestingly, studies with SH-SY5Y human neuroblastoma cells indicated that enrichment of their membrane cholesterol prevented association of $A\beta_{1\text{-}42}$ oligomers with GM1 [19]. While this may appear contradictory to the observations about cholesterol concentration and AD discussed in the previous paragraph, the effect of alteration in the cholesterol content of lipid rafts may depend upon the compensatory changes it induces.

Molander-Melin et al. [89] found that regional disease development in Alzheimer brains correlated with increased density of the gangliosides GM1 and GM2 and loss of cholesterol in lipid rafts, while Blennow et al. [13] found increases in GM1 and GD1a accompanied by decreases in GD1b and GT1b in individuals with probable AD. Changes in ganglioside composition similar to those noted in human AD were also observed in different transgenic mouse models of AD (see [4], for a recent review). Interestingly, GM1 but not GA1, has been shown to inhibit $A\beta_{1\text{-}40}$-induced release of pro-inflammatory cytokines [5]. GM1 was also found to inhibit neuronal apoptotic cell death by modulating the interaction of nerve growth factor with TrkA [27,28]. In agreement with these observations is the finding that GD3 synthase minus mice that have elevated amounts of GM1 as a result, behave like normal wild-type animals [11]. These observations may account for why a defined amount of GM1 infused intracerebroventricularly into the brains of AD patients appeared to have a positive effect [6,138].

A connection has been made between the accumulation of aggregated β-amyloid and neurofibrillary tangles composed of hyperphosphorylated tau. This relates to the observation that Aβ induces activation of the tyrosine kinase fyn in neuronal cultures [151] which catalyzes phosphorylation of tyr 18 on tau [12]. Addition of Aβ diffusible ligands (soluble Aβ oligomers) to primary neuronal cell cultures was found to result in binding of Aβ to cells in a manner similar to that seen with CTxB over time. Redistribution of the Aβ to lipid rafts was accompanied by recruitment of excess fyn to the rafts as well as further recruitment of tau. Using cells from fyn−/− mice it was found that Aβ alone was not sufficient to cause cell death. That required the presence of fyn and the recruitment of fyn and tau [151]. The neurotoxicity presumably reflects the effect of tau-induced changes in the actin cytoskeleton [32] and the ability of tau to enhance the kinase activity of fyn [121].

In addition to the aforementioned effects of GM1, plasma membrane-associated GM1 can affect intracellular Ca^{2+} levels in some instances by enhancing influx of extracellular Ca^{2+} [72] which might affect calcium-mediated phosphorylation of tau and APP. Hyperphosphorylation of APP can lead to increased intracellular Aβ [101] while hyperphosphorylation of tau can lead to its forming paired helical filaments that do not bind to microtubules [42]. These observations support the hypothesis that changes in the lipid composition of lipid rafts caused by exposure to apoE4-containing lipoproteins or by as yet unidentified causes, induces changes in signal transduction thereby inducing intracellular changes that lead to development of AD.

5.2. Huntington's

Huntington's disease (HD), characterized by neurodegeneration of the striatum and less so of the cerebral cortex [146], is caused by expression of a CAG trinucleotide repeat in exon 1 of the *HD* gene that results in inclusion of an elongated sequence of glutamine residues (>35) in the amino-terminal portion of the huntingtin protein (htt, [50]). Analyses of tissue and individual cells indicated that neurons tend to have longer polyglutamine sequences than glia and that these gains are more prominent in the striatum than cortex in low-grade cases and less marked in advanced cases [122]. Studies of post-synaptic membranes isolated from HD-expressing mice indicated that htt accumulated in the membranes prior to onset of symptoms and that subsequently there were progressive changes indicative of dysfunctional synaptic trafficking [136]. Subsequently, htt was shown to be associated with lipid rafts isolated from mouse brains. When mutant htt was associated with rafts it was accompanied by a significant increase in raft-associated glycogen synthase kinase 3-β which coincides with apoptotic stress [144]. Interestingly, the same researchers found that mutant htt from presymptomatic Huntington's disease knock-in mice was more strongly associated with rafts than wild type. Results of gene array analyses indicated that mutant htt inhibited expression of several genes encoding enzymes needed for cholesterol synthesis as well as expression of genes involved in vesicle trafficking and synaptic vesicle formation [129]. Mutant mice expressing the N-terminal portion of human htt, containing 115 CAG repeats [78], were shown to have abnormal expression of genes in their striatum that encoded glycosyltransferases needed for ganglioside synthesis [23] and similar results were obtained in studies of postmortem caudate samples from humans that had HD. Studies of gangliosides expressed in those samples indicated that there was an abnormal distribution of gangliosides in the caudates from people with HD compared to those from controls. Despite a significant increase in GD3, a significant decrease was seen in total ganglioside content in HD caudates as a result of decreased levels of GM1, GD1a, GD2, GD1b, GT1b, and GQ1b. The findings that (1) gangliosides can be found in lipid rafts, (2) have been implicated in Ca^{+2} transport [154], and (3) are altered in HD provide a possible basis for the disruption of Ca^{2+} signaling associated with HD [112]. The observation that mutant htt interferes with EGFR-mediated signaling [130] may reflect the alteration in ganglioside composition induced by Huntington's disease. Unidentified is the signal transduction pathway(s) the interaction of mutant htt with lipid rafts affects to induce the accompanying alterations in gene expression.

5.3. Parkinson's

Parkinson's disease is characterized by progressive loss of dopaminergic neurons and about a third of affected individuals will develop dementia in the final stages. While the majority of cases are listed as idiopathic, 10–15% have a defined genetic cause [14]. In genetic PD it is probable that the altered interaction of the mutant protein (six genes have been identified as causing the monogenic form of PD) with lipid rafts has subtle effects on signal transduction that over time contribute to destruction of nigral neurons. Support for this idea is provided by observations indicating that at least four proteins, which when mutated are associated with PD, have been found to associate with lipid rafts. The following discussion does not mitigate the possibility that the mutations affect mitochondrial function as well, it just points to a possible first step.

Missense mutations in the *leucine-rich repeat kinase 2* (*LRRK2*) gene have been identified as the cause of an autosomal dominant PD, one of the most common forms of familial PD [46]. The predominant mutant form of LRRK2 (G2019S) has increased kinase activity that causes neurotoxicity [150]. The protein (mutant and wild-type) associates with lipid rafts where the mutant has been hypothesized to interfere with normal signal transduction in a manner that leads to nigral degeneration [46].

Parkin, PINK1, and α-synuclein have also been shown to associate with lipid rafts ([26,123,68], respectively). Mutations in the gene encoding parkin are associated with an early-onset type of PD, the most prevalent of the known familial causes of PD [61]. Parkin, an E3 ubiquitin-ligase, is part of a multimeric protein complex found in lipid rafts on the synaptic plasma membrane and on post-synaptic densities [67] where it has been implicated in N-methyl-D-aspartate trafficking [51]. Familial parkin mutations have been shown to disrupt its ubiquitin-protein ligase activity resulting in failure to degrade both parkin and the GTPase, CDCrel-1 [163]. Loss of this activity may also inhibit turnover of other synaptic proteins, in time affecting signal transduction, synaptic transmission, and membrane plasticity [26]. PINK1 stands for PTEN-induced kinase, a kinase that phosphorylates serine and threonine residues on basic substrates [124]. Transgenic expression of Parkin in Drosophila was found to rescue the phenotype of those with a PINK1 loss-of-function mutation [160].

Mutations in α-synuclein were identified as the cause of a rare autosomal dominant type of PD [66,102] and overexpression of wild type α-synuclein can also cause PD [128]. While α-synuclein associates with the lipid components of lipid rafts, specifically phosphatidyl serine having oleic acid at C(1) and a polyunsaturated fatty acid at C(2) [68], mutant A30P α-synuclein disrupts that association [30] resulting in a loss of function. Recent studies showed that when α-synuclein bound to ganglioside GM1 it induced alpha helical structure within the protein and reduced formation of α-synuclein fibrils [79]. While GM1 had a similar effect on the A53T mutant of α-synuclein, it had minimal effect on the A30P mutant. These observations led Martinez et al. [79] to suggest that alteration of the GM1-raft association could induce changes in α-synuclein that contributed to symptoms associated with PD. This is also a possible explanation for why some of the people with PD responded positively in the clinical trial done to test the efficacy of GM1 for treating PD [120]. These observations emphasize the need to look at the interaction between other proteins associated with PD and GM1. Based on the foregoing discussion, it can be seen that alterations in phosphorylation of raft-associated proteins, ubiquitinylation and turnover of raft components, or the composition of lipid rafts (e.g. the effect of GM1 on α-synuclein) could have marked effects over time on cell viability and survival of dopaminergic neurons.

5.4. Amyotrophic lateral sclerosis

ALS is a neurodegenerative disease characterized by the progressive loss of function of motor neurons in the brain and spinal cord resulting in paralysis of voluntary muscles. While most cases are sporadic, about 10% are inherited. This means that the cause(s) for most ALS cases is not yet known [98]. For a recent review on the similarities and differences between animal models of ALS and human neuropathology see Kato [58]. Of particular interest when considering the possible role(s) of lipid rafts in ALS are observations that motor neurons isolated from 15-day old rat embryos are susceptible to excitotoxic insult resulting from activation of TrkB induced by interaction of brain-derived neurotrophic factor (BDNF) with its receptor [31,49]. Results of studies of the expression of BDNF in muscle samples taken from ALS patients in the early stage of the disease indicated that expression of BDNF was increased [69]. Subsequent studies using motor neurons indicated that excitotoxic insults could be reduced by inhibiting the effects of BDNF [88]. These researchers found that TrkB, the adenosine A2a G-protein-coupled receptor, and src-family kinases were present in complexes in both lipid rafts and nonlipid raft portions of cell membranes. However, disruption of lipid rafts using MβCD resulted in protection of cultured motor neurons from BDNF-induced excitotoxicity. These observations coupled with a number of published reports indicating that people with motor neuropathies may express anti-ganglioside antibodies, e.g. [3,63,87,99,133] support the need for appropriately functioning lipid rafts for normal motor neuron function. Over expression of BDNF, too little GM1, or other alterations may contribute to a slow decline in neuronal function resulting eventually in cell death.

It is interesting that in a study in which cerebellar granule cells were used, BDNF and LIGA20-GM1 were shown to prevent excitotoxicity through activation of TrkB [7]. Both BDNF and LIGA20-GM1 and to a much lesser extent GM1 were shown to prevent glutamate toxicity, an effect that was lost when an inhibitor of Trk tyrosine kinase was added [7]. If the differences in response reflect the type of neurons studied instead of differences in experimental protocols, they may provide an indication of why ALS preferentially affects motor neurons.

5.5. Prion disease

In prion diseases (transmissible spongiform encephalopathies) there is, as the name indicates, spongiform degeneration of the brain, which in addition to neuronal loss and astrogliosis, is characterized by accumulation of a modified form of the prion protein (PrP^i) [54]. Normal cellular prion protein, PrP^C, is held in lipid rafts by a glycosyl-phosphatidylinositol (GPI) anchor and the low density lipoprotein receptor-related protein 1 is required for its Cu^{2+}-dependent endocytosis [141]. In order for PrP^C to be endocytosed, it must move out of the lipid raft before it is endocytosed via clathrin-coated pits [135]. Conversion of PrP^C to the disease form can occur, albeit rarely, spontaneously as well as by inheritance of mutations within the gene encoding PrP [90]. However, the infectious route in which people acquire PrP^ias the result of eating contaminated food (e.g. beef from an infected steer), or exposure to a contaminated surgical instrument appears to receive the most attention. Strain-specific properties of PrP^is are carried in their tertiary structure. Conversion of PrP^C to PrP^i is induced by exposure to PrP^i. This induces a conformational change in the PrP^C characterized by a significant increase in β-sheet structure [104]. A cell-free conversion assay showed that in order for the conformational change to occur, the GPI-anchor had to be cleaved (phosphatidylinositol specific phospholipase C) from the PrP^C. Interestingly, both GPI-anchored and GPI-lacking PrP^C were shown to associate with lipid rafts [9]. Further conformation of the need for PrP^C to be associated with lipid rafts in order for infectious PrP^i to induce the conformational change was provided by the observation that cells grown in the presence of squalestatin to disrupt formation of lipid rafts were protected against prion neurotoxicity [10]. Squalestatin inhibits the activity of squalene synthase thereby blocking synthesis of cholesterol. Its effect was reversed by addition of water soluble cholesterol (cholesterol plus MβCD, Sigma). In terms of initial effects of PrP^i, its association with lipid rafts isolated from retinas and optic nerves was shown to induce alterations in raft-associated proteins such as synaptophysin [114]. These observations provide convincing evidence that lipid rafts have a significant role in prion diseases—not only are they needed for conversion of PrP^C to PrP^i, it appears that their disruption by PrP^i initiates the changes that lead to the phenotype associated with prion diseases.

6. Future directions

While by no means exhaustive, this review has looked at evidence supporting the possible role(s) of gangliosides and cholesterol in lipid rafts in diseases that over a prolonged period of time result in disruption of normal neuronal function. Based on the observations discussed it is evident that disruption of lipid rafts can result in altered signal transduction that over time could result in cells not being able to function normally, possibly culminating in cell death. It is also apparent that we are just starting to understand some of the errors (inborn or acquired) that induce disease-associated phenotypes. There are still many questions that need to be addressed. For example, in the foregoing discussion most of the studies were done using lipid rafts identified as detergent resistant membranes with the detergent used being Triton X-100. However, it can cause mixing of outer and inner membrane components [108] giving a mixture of raft components. Therefore, when studying the role of lipid rafts at least two distinct methods of isolation should be used (e.g. Triton X-100 and Brij 96) and the results compared. The fact that exposure to drugs such as ethanol [70,147] or cocaine [73] can induce marked changes in ganglioside composition in different areas of the brain, supports the hypothesis that exposure to specific environmental factors over time could induce changes in the lipid composition of rafts thereby initiating a specific disease, an area that could use more study. Much work needs to be done to ascertain whether specific gangliosides are needed for association of specific proteins with lipid rafts. If specific gangliosides are needed, do they interact directly with the protein or perhaps alter membrane fluidity to favor association of the protein with lipid rafts. If specific gangliosides are necessary for association of a protein with a raft, or for an enzyme to act upon the protein to give rise to a product associated with a particular disease, it would be interesting to know whether that ganglioside was localized or enriched in the area(s) of the brain affected by the disease. If so, it might help answer the question of why different phenotypes are seen for the different diseases. It could also provide a starting point for treatment. For example in AD it has been shown that GM1 can serve as a seed for accumulation of Aβ [157]. It is possible that inhibition of ganglioside synthesis by using an inhibitor such as N-butyldeoxy-galactonojirimycin would retard development of Aβ-containing plaques in AD, an approach found to reduce the severity of Sandhoff's disease (mutation in the β-subunit gene of hexosaminidase A and B results in accumulation of GM2 and asialo-GM2) in a mouse model [8].

The ability of cholesterol to modulate membrane fluidity affects movement of proteins into and out of lipid rafts. While a number of studies have looked at the effect of statins on development of AD and Parkinson's, results regarding their efficacy and safety are inconclusive [111]. While studying the effects of cholesterol depletion, its effect on expression of GM1 should be addressed since acute depletion of cholesterol using MβCD was shown to enhance expression of GM1. If GM1 expression is upregulated as a result of statin treatment the question of whether it enhances accumulation of Aβ should be addressed since GM1 has been implicated in its accumulation [156,157]. In addition to affecting membrane fluidity, changes in cholesterol concentration within lipid rafts could alter function, and presumably signal transduction. This raises the question of what effect altering cholesterol and/or ganglioside levels would have on gene expression by different cell types (tissue culture, animal models). The results might contribute to our understanding of why certain cells are affected by one type of disease and not by another: for example why expression of apoE4 appears to affect episodic memory more strongly than other cognitive functions [71]. They might also explain why different cells respond differently to neurotrophic factors as described for BDNF, and/or why treatment with GM1 appeared to help individuals with PD and AD.

The question of whether a mutation in one protein identified as a causative agent for a particular disease has a broader effect should also be addressed. An example supporting the concept that there may be commonality between some of the mechanisms causing disruption is seen in the observation that PrP^c functions in regulating cleavage of APP [96]. Overexpression of PrP^c was shown to reduce Aβ formation while lack of PrP^c resulted in an increase. An obvious question is whether such interactions have therapeutic potential. Most importantly, researchers need to identify cell-signaling changes induced by the various raft-associated changes as it is this information that will provide investigators with the basis for identifying small molecule agonists or antagonists to test as potential therapeutics.

Based on the foregoing discussion it can be seen that alterations in cholesterol and/or the ganglioside composition of lipid rafts can significantly affect cell function. Cholesterol was emphasized because of the growing amount of information indicating that alterations in its concentration damages neurons; gangliosides were chosen due to their high concentration in the gray matter of the brain, association with lipid rafts, and accumulating evidence of their involvement in diseases affecting neurodegeneration. It is anticipated that as the biological roles of these lipids are more completely defined the knowledge will be used to develop methods to inhibit the subtle changes in lipid raft composition that over time may lead to neurodegeneration and dementia. Not only would this reduce the medical burden caused by these diseases, it would enhance the quality of life for many in the aging population.

Conflict of interest

The author declares that she has no competing financial interests.

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