Mini-Review • DOI: 10.2478/v10134-010-0043-6 • Translational Neuroscience • 1(4) • 2010 • 300-307

VERSITA

Translational Neuroscience

ROLE OF GANGLIOSIDES IN BRAIN AGING AND NEURODEGENERATION

Kristina Mlinac,
Svjetlana Kalanj Bognar*

Laboratory for Molecular Neurobiology and Neurochemistry,
Croatian Institute for Brain Research,
School of Medicine,
University of Zagreb
Šalata 12, 10000 Zagreb, Croatia

Abstract

Gangliosides are membrane glycosphingolipids bearing sialic acid residues. Within membranes, gangliosides are specifically enriched in highly organized domains, lipid rafts, and are attributed with diverse functions such as intercellular interactions, cell recognition, neurotransmission, and signal transduction. The highest concentration and variability of ganglioside structures are found in the human brain. Specific temporal and regional distribution of brain gangliosides has been reported; moreover, gangliosides may serve as markers of neurodevelopmental stages, aging and neurodegeneration. Brain ganglioside content and composition as well as ganglioside metabolism are altered in Alzheimer's disease. It appears that the alterations of ganglioside metabolism leading to changes in membrane physico-chemical properties are not merely a consequence of primary pathology, but may also be involved in the early pathogenesis of Alzheimer's disease through documented effects on APP proteolytic processing and amyloid aggregation. Investigations of glycolipid metabolic alterations which accompany neurodegenerative disorders provide insight into pathogenetic mechanisms and enable recognition of diagnostic markers as well as molecular structures acting as therapeutic tools interfering with cascade of pathological events.

Keywords

Gangliosides • Brain • Aging • Neurodegeneration

Received 26 November 2010
accepted 16 December 2010

1. Introduction

Gangliosides are a diverse class of glycosphingolipids found in all mammalian membranes, although they are especially abundant in neural tissue. These amphipathic molecules consist of a hydrophobic ceramide core anchoring a polar carbohydrate chain, bearing one or more sialic acid residues in the outer leaflet of the plasma membrane (Figure 1) [1]. Several hundreds of ganglioside structures have been characterized based on differences in either the oligosaccharide chain, or the fatty acids linked to the ceramide moiety of the molecule [2]. Individual ganglioside species are present at distinct time periods during neurodevelopment, brain maturation and aging; ganglioside expression patterns change dramatically during those processes [3-5], as well as during certain pathological conditions [6-10]. In the adult human brain, there is also a specific regional distribution of gangliosides as evidenced by the extensive biochemical analysis of forty brain samples - consisting of neocortical, archicortical, and paleocortical areas, telencephalic, diencephalic, and mesencephalic subcortical nuclei, cerebellum, and corresponding white matter bundles - revealing remarkable regional pattern differences [11]. Briefly, preponderance of a-series gangliosides (GD1a, GM1) was found in frontal, parietal and temporal cortical areas, while occipital cortex and structures related to visual system were characterized by higher proportion of b-series gangliosides (GQ1b, GT1b, GD1b). Predominance of b-series gangliosides was found in cerebellum, and of a-series gangliosides in hippocampal archicortex and the amygdala [11]. Due to their regional and temporal distribution, gangliosides can serve as neurodevelopmental and aging markers as well as biomarkers for specific pathological processes [4,5,12].

Gangliosides are not distributed evenly throughout the plasma membrane, but rather concentrated into organized microdomains termed lipid rafts [13]. In addition to gangliosides and other glycosphingolipids, lipid rafts are enriched in cholesterol and specific membrane proteins making those regions different in both composition and molecular organization from the rest of the membrane. For that reason lipid rafts are considered to be signaling platforms important as a site for the interaction between glycosphingolipids and signaling molecules [14].

2. Ganglioside metabolism

Gangliosides are synthesized by a stepwise addition of monosaccharides to lactosylceramide by glycotransferases in the Golgi apparatus and are then transported to the outer leaflet of the plasma membrane [15]. The first ganglioside in the biosynthetic pathway is GM3 which is then modified to give a-, b- and c-series gangliosides (Figure 2). Since gangliosides are essential for normal cell function, disorders in their biosynthetic

* *E-mail: svjetla@mef.hr*

pathway resulting in the depletion of certain gangliosides were thought to be lethal. However, this assumption was disproved when a mutation in the biosynthetic enzyme GM3 synthase in humans was found to result in the loss of expression of complex gangliosides, causing infantile-onset symptomatic epilepsy syndrome [16]. In addition, various experimental mouse models with blocks in ganglioside synthesis were produced to investigate the physiological roles of gangliosides [17] which led to the elucidation of numerous ganglioside functions. The main observations in studies on genetically modified mice include: (a) blocking ganglioside biosynthetic pathways at specific synthetic steps leads to alteration in ganglioside stuctures and composition, however, the total quantity of gangliosides is maintained due to replacement of more complex gangliosides by simpler structures; (b) deficiency and/or accumulation of specific gangliosides structures, depending on the site of block in synthesis, has very different phenotypic consequences mostly related to neurological abnormalities [18].

Historically, the catabolism of gangliosides has been more extensively investigated than ganglioside biosynthesis. Degradation of gangliosides is a sequential process that occurs on the surface of cell membranes, starting at the plasma membrane by the action of membrane sialidase which hydrolyses poly-sialo gangliosides to GM1. After the removal of GM1 and other gangliosides from the plasma membrane by endocytosis they are further degraded in lysosomes where they are embedded in the intralysosomal membrane [19]. Carbohydrate residues are sequentially released by the action of different glycosidases until they are degraded to ceramide (Figure 3), which is then cleaved into sphingosine and fatty acid. Many genetic defects of enzymes involved in endo-lysosomal catabolic pathways have been described in humans. Deficiencies of the enzymes involved in ganglioside degradation lead to the accumulation of specific non-degraded sphingolipid species, which results in lysosomal storage disorders with devastating effects [20].

Complex regulation of ganglioside metabolism has not been explained in details although several mechanisms, based on *in vivo* and *in vitro* observations, have been suggested: transcriptional regulation of genes involved in ganglioside metabolism; proper sorting and directing of glycosphingolipid structures into cellular compartments; feed-back control of metabolism; and enzyme posttranslational modifications [21].

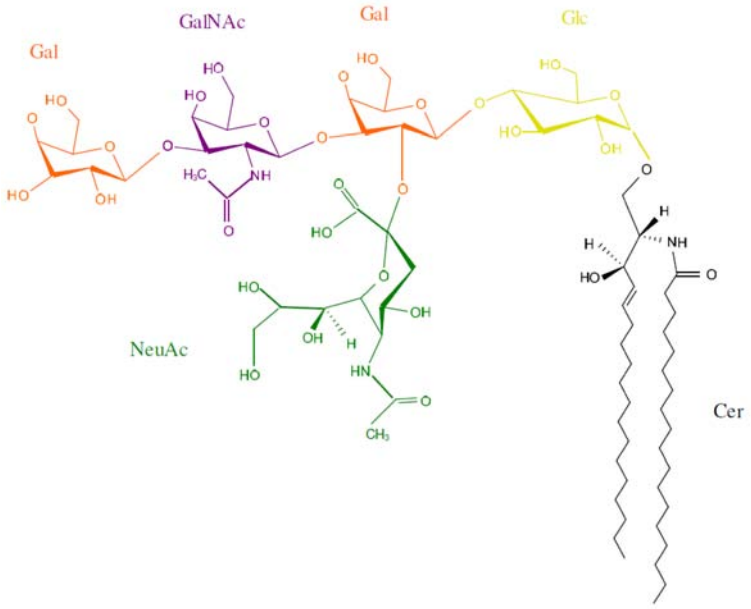

Figure 1. Structure of ganglioside GM1.

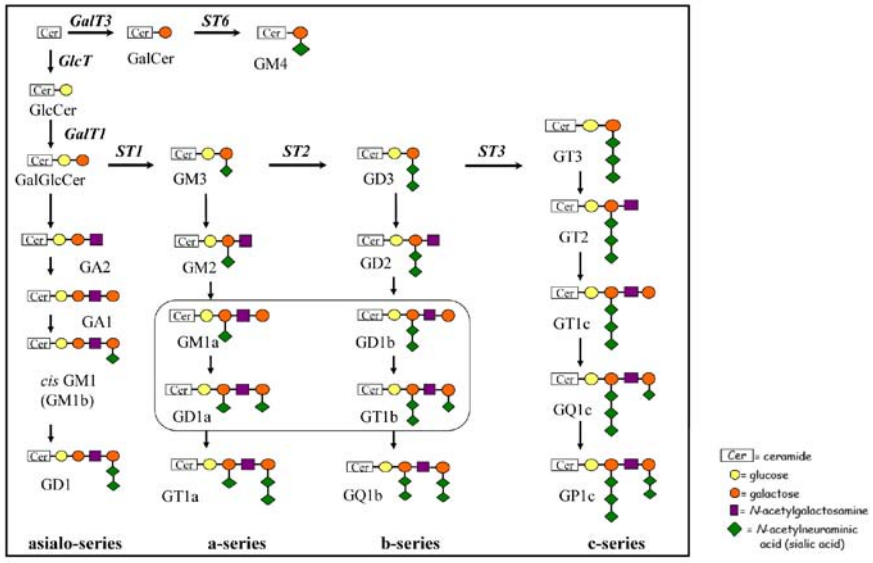

Figure 2. Schematic representation of ganglioside biosynthesis. Cer=ceramide; Glc=glucose; Gal=galactose; *GlcT*=glucosyltransferase; *ST1*=sialyltransferase I (GM3-synthase); *ST2*=sialyltransferase II (GD3-synthase); *ST3*=sialyltransferase III (GT3-synthase); *ST6*=sialyltransferase VI (GM4-synthase). Abbreviations for ganglioside structures are given acccording to Svennerhom nomenclature [76]. Major brain gangliosides are boxed.

3. Ganglioside functions

The membrane localisation of gangliosides allows them to interact laterally, within the membrane plane, with other lipids and membrane proteins such as receptor kinases [22]. Also, because of the oligosaccharide chain protruding towards the extracellular space, gangliosides can communicate with other cells through specific intermolecular interactions [23]. Thanks to *cis* and *trans* interactions gangliosides exert their effects on many physiological processes (Table 1) and are crucial for proper functioning of the central nervous system [24]. One illustration of ganglioside interactions with other cells (*trans*), influencing nervous system stability, is the interaction between axons and myelin, multilayered complex membrane that wraps the nerve axons and is required for rapid nerve conductance. Myelin-associated glycoprotein (MAG) is a sialic acid binding lectin expressed in myelin-producing cells directly opposed to the surface of the axon [25]. It has been shown that MAG binds to major nerve gangliosides GD1a and GT1b [26] thus promoting their

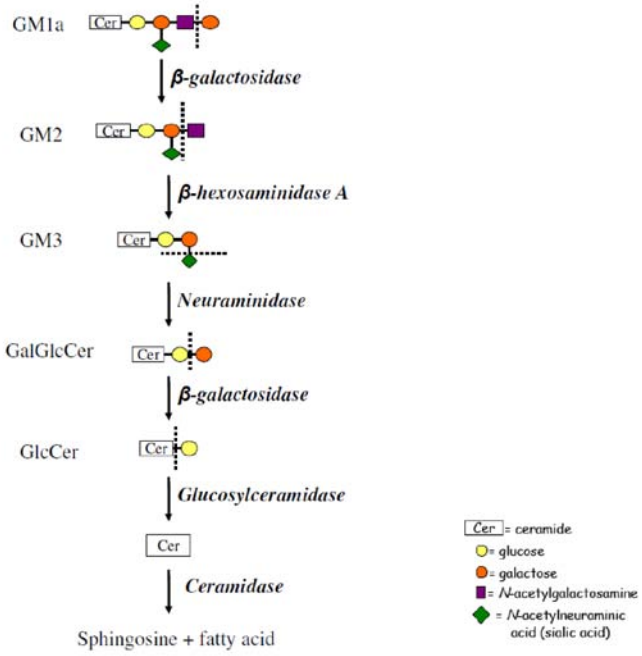

Figure 3. Schematic representation of major pathway of ganglioside degradation in lysosomes. Cer=ceramide; Glc=glucose; Gal=galactose. Ganglioside abbreviations are given acccording to Svennerholm [76].

Table 1. Diversity of gangliosides functions.

MAG – myelin-associated glycoprotein; PDGF – platelet-derived growth factor; NMDA – *N*-methyl-D-aspartate

Gangliosides and intercellular communication			Gangliosides within cell membrane			Gangliosides and intracellular events		
Effect	Example	Ref	Effect	Example	Ref	Effect	Example	Ref
Myelin-axon interactions	GD1a and GT1b are functional ligands for MAG	[23]	Modulation of membrane proteins activity	Local accumulation of GM1 changes the microenvironment and displaces PDGF receptor and blocks the PDGF signaling	[28]	Proliferation	GD1b and GT1b enhance proliferation through continuous activation of TrkA and ERK1/2	[72]
Cell adhesion and migration	GM3 inhibits cell migration on fibronectin	[69]		Interaction of GM3 with the insulin receptor which leads to insulin resistance (inhibition of signaling)	[29]	Differentiation	GM1 promotes neuritogenesis by modulating Ca^{2+} flux in the cell	[73]
Ligands for neurotransmitters	GM1 binds to serotonin released from synaptic vesicles	[31]		GM1 and GQ1b have a stimulatory role in functional coupling between adenylate cyclase and serotonin receptors	[71]	Apoptosis	GD3 induces apoptosis; it causes opening of the mitochondrial permeability transition pore complex and the release of apoptogenic factors	[74]
Pathogen binding	GT1b and GQ1b are ligands for botulinum neurotoxin	[70]		GQ1b activates the NMDA receptor signaling pathway by increasing tyrosine phosphorylation of one of its subunits	[30]	Regeneration	GT1b promotes regeneration of lesioned hypoglossal nerve	[75]

physical association with the neurotrophin receptor ($p75^{NTR}$) to lipid rafts and induces signal transduction and inhibition of neurite outgrowth [27]. Because of their role as functional MAG ligands, gangliosides are thought to be extremely important in myelin stability.

In addition to other intercellular communication functions, gangliosides have a well-recognized role in modulating the activity of membrane proteins, such as receptor kinases. Their impact on cell signaling pathways may be accomplished on several levels: 1) through changing the microenvironment (membrane/lipid raft composition) [28]; 2) through direct interactions with membrane proteins [29,30]; and 3) through binding ligands and exposing them to their receptors in a specific orientation, or through the disabling formation of aggregates of ligand molecules [31,32]. Furthermore, gangliosides are involved in processes such as cellular proliferation, differentiation and programmed cell death (summarized in Table 1), as well as in oncogenic transformation. Namely, distinct ganglioside expression pattern and unusual ganglioside species have been shown in brain tumors [33] indicating an alteration in the ganglioside biosynthetic pathway during tumorigenesis. In addition, higher expression of specific ganglioside biosynthetic enzymes has been linked with proliferation and tumor growth, as evidenced for GD3 synthase which enhances tumorigenicity in breast cancer through constitutive activation of certain signaling pathways [34]. Interestingly, elimination of the same enzyme has been found to improve memory and reduce amyloid-β plaque load in APP/PSEN1 transgenic mice [35].

4. Gangliosides in brain aging and neurodegeneration

Considering the abundance and structural diversity of glycosphingolipids in mammalian brain tissue, their involvement in brain development, aging and neurodegeneration is not surprising. The importance of membrane lipid raft constituents in neurodevelopmental phenomena is asserted by the observation that neuronal lipid rafts are specifically positioned in axonal plasma membranes, where they link to molecules of the extracellular matrix through intermolecular interactions [36,37]. The integrity of vast surfaces of extremely complex membranes in the nervous system is vital for its normal functions because some of the biochemical and physiological phenomena underlying specific functions of adult brain are associated with membranes – nerve conductance, neurotransmitter transmission, signal transduction. Moreover, processes such as cell proliferation and differentiation (occuring during brain development), neuritogenesis, axonal sprouting, synaptogenesis, myelination, require a formation of different specialized membrane structures and these may also modify structural and functional plasticity of neural cells.

Quantitative and qualitative changes of brain gangliosides pattern, as previously stated, may indeed serve as stage specific markers of mammalian brain development and aging [4,5]. Both biochemical and immunohistochemical characterization evidenced that: GD3 is specific for proliferating cells; polysialylated c-series gangliosides are synthesized during early neurodevelopmental stages yet are found in modest quantities in adult brain; GM1, GD1b and GT1b are abundant during neurogenesis, neuronal migration and neuritogenesis, as well as in adult brain; GD1a is found in high proportion during synaptogenesis; increase in GM1 and GM4 accompanies gliogenesis and myelination [4,5].

During aging and neurodegeneration processes, physico-chemical properties of membranes change as a consequence of altered proportion of lipids in membranes and/or changed ratio of membrane lipids; in addition, the functions of specific membrane proteins may be altered due to changes in their interactions with lipid molecules. The systematic study of lipid content in human brain during aging showed no dramatic loss of the main lipid classes (glycosphingolipids, phospholipids, cholesterol) from 20 to 80 years of age; however, an alteration in the pattern of lipid molecules (particularly gangliosides) was observed [38]. Changes in ganglioside content and pattern have shown to be more expressed in brain tissue affected with neurodegeneration (Alzheimer's disease, AD). Several studies have documented a significant decrease in the total concentration of gangliosides in AD brain samples compared with age-matched controls. In addition, the composition of gangliosides differed in AD brain samples from the frontal, parietal and temporal cortices, showing a decreased proportion of ganglio-series gangliosides (GD1a, GD1b, GT1b) and an increase in simple ganglioside structures (GM2, GM3, GM4) [6,7,39,40]. The quantitative and qualitative alterations of gangliosides in AD brain have been explained as a consequence of neuronal cell degeneration, demyelination and gliosis. The finding of an increased proportion of simple gangliosides also indicated accelerated degradation of brain gangliosides in AD [7]. The speculation on accelerated lysosomal degradation of gangliosides in AD brain tissue has been supported by reported immunohistochemical studies, showing both abnormal distribution and colocalization of several lysosomal hydrolases and proteases (β-hexosaminidase A, α-glucosidase, catepsin D) with β–amyloid in diffuse plaques in cerebellum and striatum in AD and Down's syndrome (DS) brain tissue [41]. Documented increases in the expression of lysosomal hydrolases in neuronal populations affected by amyloid pathology has been explained by the up-regulation of the endosomal-lysosomal system and has been proposed to be an early marker of metabolic dysfunction related to primary AD etiopathogenesis. Similar biochemical alterations have been observed in AD peripheral tissues, supporting the hypothesis on probable systemic nature of Alzheimer's disease. Several groups have reported on alterations of glycosphingolipid metabolism in AD peripheral cells: (1) Maguire and colleagues found decreased activity of GSL biosynthetic enzymes (sialyltransferases) in serum and brain tissue in AD as compared with control samples [42,43]; (2) our group showed statistically significant increase in β–galactosidase activity in AD leukocytes in comparison with age-matched control and increased activity of β–galactosidase and β–hexosaminidase in AD skin fibroblast cell line and age-matched controls, indicating that

acceleration of at least some lysosomal catabolic pathways of gangliosides is present in AD nonneural cells (leukocytes and skin fibroblasts) [44]; (3) Emiliani determined up-regulation of lysosomal hydrolases (β-galactosidase, β-hexosaminidase) in skin fibroblasts derived from both familial and sporadic AD patients; in this paper, Ras activation was suggested to play a role in transcriptional up-regulation of analyzed lysosomal glycohydrolases in AD skin fibroblasts [45]; (4) Pitto reported enhanced GM1 catabolism in AD skin fibroblasts and proposed that increased hydrolysis rate of sphingolipids could serve as peripheral biochemical hallmark of the disease [46].

The results of the aforementioned studies call attention to the possible involvement of membrane lipids (glycosphingolipids, cholesterol) and lipid rafts in complex pathogenesis of Alzheimer's disease [47-49]. The idea that cholesterol is linked to pathogenesis of Alzheimer's disease (AD) was first introduced by the observation that specific genetic polymorphism for apolipoprotein E gene (APOE allele 4) increased the risk for developing the disease [50]. Biochemical studies have shown that apolipoprotein E is actually involved in the trafficking and sorting of amyloid precursor protein, whose abnormal processing leads to AD pathology [51]. However, the fact that apolipoprotein E is involved in lipid metabolism, and also that therapy with statins (drugs inhibiting the crucial enzyme in cholesterol biosynthesis) alleviates the clinical symptoms and progression of the disease, has initiated a new line of research focused on cholesterol and its possible roles in AD pathogenesis [47,48,52]. The results of relevant studies have supported this idea: changes in cholesterol content and trafficking have been found in Alzheimer's disease [53-56]; the control of cholesterol and sphingomyelin metabolism involves processing of the amyloid precursor protein (APP) [57]; and gene expression analysis has also shown that the cluster of genes involved in lipid metabolism (also of genes involved in extracelullar matrix molecules synthesis) is upregulated in hippocampal samples in Alzheimer's disease [58].

Lipid rafts are involved in regulation of trafficking and proteolytic processing of APP [59]. It appears that amyloidogenic APP processing occurs within the rafts; thus the content and composition of cholesterol and glycosphingolipids critically influences the formation of amyloidogenic Aβ-peptide [60]. Moreover, the conformational change and resulting aggregation of Aβ is dependent on its interaction with specific molecules of the lipid bilayer [61]. It has been shown that ganglioside GM1 acts as an endogenous seed for amyloidogenesis, interacting with amyloid protein, and that sterols (cholesterol) may promote the formation of GM1 clusters, which interact with Aβ [62,63]. Preferential binding of Aβ to GM1 and formation of GAβ as well as neurotoxicity of amyloid fibrils in the presence of gangliosides have been demonstrated by *in vivo* and *in vitro* studies [64]. A growing body of evidence confirms that Aβ binding to gangliosides in cell membranes may be the initial step in Aβ polymerization and thus is an important contributing factor in AD pathogenesis. Additional supporting evidence on GM1 availability for GAβ formation comes from a study reporting increased proportions of gangliosides GM1 and GM2 in lipid domains isolated from AD frontal and temporal cortex [65]. We suggest that GM1 clustering, which is a prerequisite for GAβ generation inside and on the surface of neurons in AD, is a consequence of cellular death and atrophy accompanied by the accelerated degradation of membrane glycosphingolipids (Figure 4). Namely, ganglioside catabolism begins at the membrane, where more complex membrane gangliosides are being degraded by sialidase (neuraminidase). The product of the membrane sialidase activity is GM1, which is then internalized into an endosomal-lysosomal compartment.

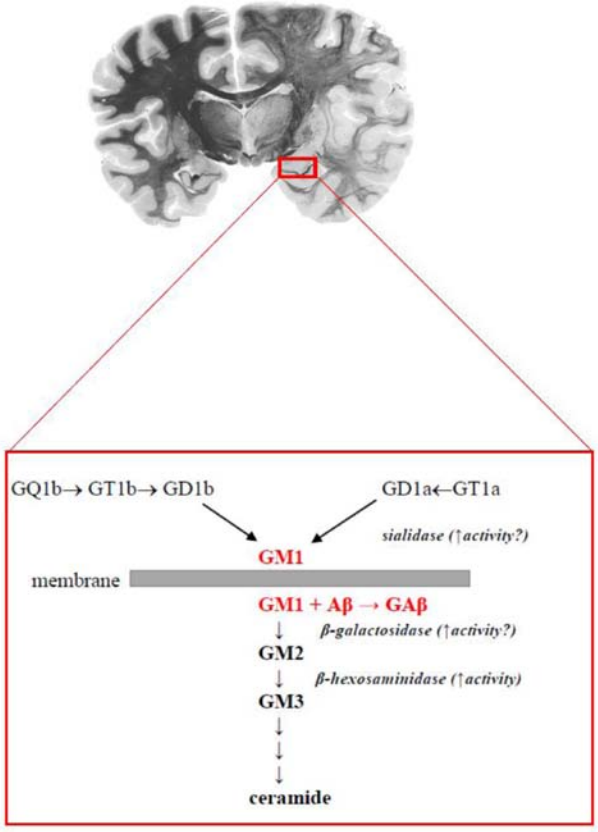

Figure 4. Ganglioside GM1 is accumulated due to degradation of complex gangliosides by sialidase activity. Increased activity of β–hexosaminidase was documented in AD brain [41], while increased activity of β –galactosidase and β –hexosaminidase was shown in non-neural cells in AD [44]. Activity of sialidase and β–galactosidase is probably increased in AD brain. Higher concentration of ceramide is associated with APP secretion and Aβ production [59].

Besides being involved in regulation of APP processing and Aβ aggregation, sphingolipids are also important for the regulation of neuronal excitability and synaptic activity [66,67]. Alteration in sphingolipid metabolism in AD results in the disturbance of intramembraneous lipid-lipid and lipid-protein interactions which may underlie alterations in complex cellular signalisation events and probably those pathways which are asccociated with synaptic plasticity [59]. In addition, it has been documented that sphinogolipids may regulate formation of the SNARE complex, the fusion of synaptic vesicles with target membranes, and exocytosis, i.e. events involved in neurotransmission [68]. It can be suggested that alterations of sphingolipid metabolism in AD are also related to disturbed synaptic activity, through sphingolipid mediated regulation of presynaptic and postsynaptic events.

In conclusion, numerous studies have confirmed that gangliosides are involved in aging and neurodegeneration. The role of gangliosides in the complex pathogenesis of neurodegeneration is associated with the localization of these lipid molecules in membranes, particularly in highly organized lipid rafts. It seems that alterations in ganglioside metabolism leading to changes in membrane physico-chemical properties are not merely a consequence of primary pathology, but may be involved in the early pathogenesis of the disease through documented effects on APP proteolytic processing and amyloid aggregation. Investigations of glycolipid metabolic alterations which accompany neurodegenerative disorders give insight into pathogenetic mechanisms and enable recognition of diagnostic markers as well as molecular structures acting as therapeutic tools interfering with cascade of pathological events.

Acknowledgments

The work was done within project financed by Croatian Ministry of Science, Education and Sport (108-1081870-1877).

Abbreviations

AD	– Alzheimer's disease
Aβ	– amyloid-β peptide
APOE4	– apolipoprotein E gene allele 4
APP	– amyloid precursor protein
Cer	– ceramide
Gal	– galactose
GalNAc	– *N*-acetylgalactosamine
Glc	– glucose
GlcT	– glucosyltransferase
GSL	– glycosphingolipid
DS	– Down's syndrome
MAG	– myelin-associated glycoprotein
NeuAc	– *N*-acetylneuraminic acid (sialic acid)
NMDA	– *N*-methyl-D-aspartate
$P75^{NTR}$	– neurotrophin receptor
PDGF	– platelet-derived growth factor
PSEN1	– presenilin1
SNARE	– SNAP (Soluble NSF Attachment Protein) Receptors
ST	– sialyltransferase

References

[1] Li Y.T., Li S.C., Biosynthesis and catabolism of glycosphingolipids, Adv. Carbohydr. Chem. Biochem., 1982, 40, 235-288

[2] Yamakawa T., Thus started ganglioside research, Trends Biochem. Sci., 1988, 13, 452-454

[3] Svennerholm L., Bostrom K., Jungbjer B., Olsson L., Membrane lipids of adult human brain: lipid composition of frontal and temporal lobe in subjects of age 20 to 100 years, J. Neurochem., 1994, 63, 1802-1811

[4] Rosner H., Developmental expression and possible roles of gangliosides in brain development, Prog. Mol. Subcell. Biol., 2003, 32, 49-73

[5] Kracun I., Rosner H., Drnovsek V., Vukelic Z., Cosovic C., Trbojevic-Cepe M., et al., Gangliosides in the human brain development and aging, Neurochem. Int., 1992, 20, 421-431

[6] Crino P.B., Ullman M.D., Vogt B.A., Bird E.D., Volicer L., Brain gangliosides in dementia of the Alzheimer type, Arch. Neurol., 1989, 46, 398-401

[7] Kracun I., Kalanj S., Talan-Hranilovic J., Cosovic C., Cortical distribution of gangliosides in Alzheimer's disease, Neurochem. Int., 1992, 20, 433-438

[8] Kamp P.E., den Hartog Jager W.A., Maathuis J., de Groot P.A., de Jong J.M., Bolhuis P.A., Brain gangliosides in the presenile dementia of Pick, J. Neurol. Neurosurg. Psychiatry, 1986, 49, 881-885

[9] Desplats P.A., Denny C.A., Kass K.E., Gilmartin T., Head S.R., Sutcliffe J.G., et al., Glycolipid and ganglioside metabolism imbalances in Huntington's disease, Neurobiol. Dis., 2007, 27, 265-277

[10] Varki N.M., Varki A., Diversity in cell surface sialic acid presentations: implications for biology and disease, Lab Invest, 2007, 87, 851-857

[11] Kracun I., Rosner H., Cosovic C., Stavljenic A., Topographical atlas of the gangliosides of the adult human brain, J. Neurochem., 1984, 43, 979-989

[12] Yin J., Miyazaki K., Shaner R.L., Merrill A.H., Jr., Kannagi R., Altered sphingolipid metabolism induced by tumor hypoxia - new vistas in glycolipid tumor markers, FEBS Lett., 2010, 584, 1872-1878

[13] Simons K., Ehehalt R., Cholesterol, lipid rafts, and disease, J. Clin. Invest, 2002, 110, 597-603

[14] Allende M.L., Proia R.L., Lubricating cell signaling pathways with gangliosides, Curr. Opin. Struct. Biol., 2002, 12, 587-592

[15] Kolter T., Proia R.L., Sandhoff K., Combinatorial ganglioside biosynthesis, J. Biol. Chem., 2002, 277, 25859-25862

[16] Simpson M.A., Cross H., Proukakis C., Priestman D.A., Neville D.C., Reinkensmeier G., et al., Infantile-onset symptomatic epilepsy syndrome caused by a homozygous loss-of-function mutation of GM3 synthase, Nat. Genet., 2004, 36, 1225-1229

[17] Furukawa K., Tokuda N., Okuda T., Tajima O., Furukawa K., Glycosphingolipids in engineered mice: insights into function, Semin. Cell Dev. Biol., 2004, 15, 389-396

[18] Schnaar R.L., Brain glycolipids:insights from genetic modifications of biosynthetic enzymes, In: Fukuda M, Rutishauser U., Schnaar R.L. (Eds.), Neuroglycobiology, Oxford University Press Inc., New York, 2005

[19] Kolter T., Sandhoff K., Lysosomal degradation of membrane lipids, FEBS Lett., 2010, 584, 1700-1712
[20] Wennekes T., van den Berg R.J., Boot R.G., van der Marel G.A., Overkleeft H.S., Aerts J.M., Glycosphingolipids--nature, function, and pharmacological modulation, Angew. Chem. Int. Ed Engl., 2009, 48, 8848-8869
[21] Yu R.K., Bieberich E., Xia T., Zeng G., Regulation of ganglioside biosynthesis in the nervous system, J. Lipid Res., 2004, 45, 783-793
[22] Lopez P.H., Schnaar R.L., Gangliosides in cell recognition and membrane protein regulation, Curr. Opin. Struct. Biol., 2009, 19, 549-557
[23] Schnaar R.L., Brain gangliosides in axon-myelin stability and axon regeneration, FEBS Lett., 2010, 584, 1741-1747
[24] Kawai H., Allende M.L., Wada R., Kono M., Sango K., Deng C., et al., Mice expressing only monosialoganglioside GM3 exhibit lethal audiogenic seizures, J. Biol. Chem., 2001, 276, 6885-6888
[25] Quarles R.H., Myelin-associated glycoprotein (MAG): past, present and beyond, J. Neurochem., 2007, 100, 1431-1448
[26] Collins B.E., Kiso M., Hasegawa A., Tropak M.B., Roder J.C., Crocker P.R., et al., Binding specificities of the sialoadhesin family of I-type lectins. Sialic acid linkage and substructure requirements for binding of myelin-associated glycoprotein, Schwann cell myelin protein, and sialoadhesin, J. Biol. Chem., 1997, 272, 16889-16895
[27] Fujitani M., Kawai H., Proia R.L., Kashiwagi A., Yasuda H., Yamashita T., Binding of soluble myelin-associated glycoprotein to specific gangliosides induces the association of p75NTR to lipid rafts and signal transduction, J. Neurochem., 2005, 94, 15-21
[28] Mitsuda T., Furukawa K., Fukumoto S., Miyazaki H., Urano T., Furukawa K., Overexpression of ganglioside GM1 results in the dispersion of platelet-derived growth factor receptor from glycolipid-enriched microdomains and in the suppression of cell growth signals, J. Biol. Chem., 2002, 277, 11239-11246
[29] Yamashita T., Hashiramoto A., Haluzik M., Mizukami H., Beck S., Norton A., et al., Enhanced insulin sensitivity in mice lacking ganglioside GM3, Proc. Natl. Acad. Sci. U. S. A, 2003, 100, 3445-3449
[30] Jung W.R., Kim H.G., Shin M.K., Park D.I., Kim K.L., The effect of ganglioside GQ1b on the NMDA receptor signaling pathway in H19-7 cells and rat hippocampus, Neuroscience, 2010, 165, 159-167
[31] Fantini J., Barrantes F.J., Sphingolipid/cholesterol regulation of neurotransmitter receptor conformation and function, Biochim. Biophys. Acta, 2009, 1788, 2345-2361
[32] Posse de C.E., Sipione S., Sphingolipids and gangliosides of the nervous system in membrane function and dysfunction, FEBS Lett., 2010, 584, 1748-1759
[33] Vukelic Z., Kalanj-Bognar S., Froesch M., Bindila L., Radic B., Allen M., et al., Human gliosarcoma-associated ganglioside composition is complex and distinctive as evidenced by high-performance mass spectrometric determination and structural characterization, Glycobiology, 2007, 17, 504-515
[34] Cazet A., Lefebvre J., Adriaenssens E., Julien S., Bobowski M., Grigoriadis A., et al., GD synthase expression enhances proliferation and tumor growth of MDA-MB-231 breast cancer cells through c-Met activation, Mol. Cancer Res., 2010, 8, 1526-1535
[35] Bernardo A., Harrison F.E., McCord M., Zhao J., Bruchey A., Davies S.S., et al., Elimination of GD3 synthase improves memory and reduces amyloid-beta plaque load in transgenic mice, Neurobiol. Aging, 2009, 30, 1777-1791
[36] Kappler J., Baader S.L., Franken S., Pesheva P., Schilling K., Rauch U., et al., Tenascins are associated with lipid rafts isolated from mouse brain, Biochem. Biophys. Res. Commun., 2002, 294, 742-747
[37] Freire E., Gomes F.C., Jotha-Mattos T., Neto V.M., Silva Filho F.C., Coelho-Sampaio T., Sialic acid residues on astrocytes regulate neuritogenesis by controlling the assembly of laminin matrices, J. Cell Sci., 2004, 117, 4067-4076
[38] Svennerholm L., Boström K., Fredman P., Månsson J.E., Rosengren B., Rynmark B.M., . Human brain gangliosides: developmental changes from early fetal stage to advanced age, Biochim. Biophys. Acta, 1989, 1005, 109-117
[39] Kalanj S., Kracun I., Rosner H., Cosovic C., Regional distribution of brain gangliosides in Alzheimer's disease, Neurol. Croat., 1991, 40, 269-281
[40] Svennerholm L., Ganglioside loss is a primary event in Alzheimer disease type I, Prog. Brain Res., 1994, 101, 391-404
[41] Cataldo A.M., Barnett J.L., Mann D.M., Nixon R.A., Colocalization of lysosomal hydrolase and beta-amyloid in diffuse plaques of the cerebellum and striatum in Alzheimer's disease and Down's syndrome, J. Neuropathol. Exp. Neurol., 1996, 55, 704-715
[42] Maguire T.M., Breen K.C., A decrease in neural sialyltransferase activity in Alzheimer's disease, Dementia, 1995, 6, 185-190
[43] Maguire T.M., Gillian A.M., O'Mahony D., Coughlan C.M., Dennihan A., Breen K.C., A decrease in serum sialyltransferase levels in Alzheimer's disease, Neurobiol. Aging, 1994, 15, 99-102
[44] Kalanj-Bognar S., Rundek T., Furac I., Demarin V., Cosovic C., Leukocyte lysosomal enzymes in Alzheimer's disease and Down's syndrome, J. Gerontol. A Biol. Sci. Med. Sci., 2002, 57, B16-B21
[45] Emiliani C., Urbanelli L., Racanicchi L., Orlacchio A., Pelicci G., Sorbi S., et al., Up-regulation of glycohydrolases in Alzheimer's Disease fibroblasts correlates with Ras activation, J. Biol. Chem., 2003, 278, 38453-38460
[46] Pitto M., Raimondo F., Zoia C., Brighina L., Ferrarese C., Masserini M., Enhanced GM1 ganglioside catabolism in cultured fibroblasts from Alzheimer patients, Neurobiol. Aging, 2005, 26, 833-838
[47] Han X., Lipid alterations in the earliest clinically recognizable stage of Alzheimer's disease: implication of the role of lipids in the pathogenesis of Alzheimer's disease, Curr. Alzheimer Res., 2005, 2, 65-77
[48] Koudinov A.R., Koudinova N.V., Cholesterol homeostasis failure as a unifying cause of synaptic degeneration, J. Neurol. Sci., 2005, 229-230, 233-240

[49] Ariga T., McDonald M.P., Yu R.K., Role of ganglioside metabolism in the pathogenesis of Alzheimer's disease--a review, J. Lipid Res., 2008, 49, 1157-1175

[50] Corder E.H., Saunders A.M., Strittmatter W.J., Schmechel D.E., Gaskell P.C., Small G.W., et al., Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families, Science, 1993, 261, 921-923

[51] Runz H., Rietdorf J., Tomic I., de Bernard M., Beyreuther K., Pepperkok R., et al., Inhibition of intracellular cholesterol transport alters presenilin localization and amyloid precursor protein processing in neuronal cells, J. Neurosci., 2002, 22, 1679-1689

[52] Fassbender K., Simons M., Bergmann C., Stroick M., Lutjohann D., Keller P., et al., Simvastatin strongly reduces levels of Alzheimer's disease beta -amyloid peptides Abeta 42 and Abeta 40 in vitro and in vivo, Proc. Natl. Acad. Sci. U. S. A, 2001, 98, 5856-5861

[53] Mattson M.P., Cutler R.G., Jo D.G., Alzheimer peptides perturb lipid-regulating enzymes, Nat. Cell Biol., 2005, 7, 1045-1047

[54] Gylys K.H., Fein J.A., Yang F., Miller C.A., Cole G.M., Increased cholesterol in Abeta-positive nerve terminals from Alzheimer's disease cortex, Neurobiol. Aging, 2007, 28, 8-17

[55] Levi O., Lutjohann D., Devir A., von B.K., Hartmann T., Michaelson D.M., Regulation of hippocampal cholesterol metabolism by apoE and environmental stimulation, J. Neurochem., 2005, 95, 987-997

[56] Spell C., Kolsch H., Lutjohann D., Kerksiek A., Hentschel F., Damian M., et al., SREBP-1a polymorphism influences the risk of Alzheimer's disease in carriers of the ApoE4 allele, Dement. Geriatr. Cogn Disord., 2004, 18, 245-249

[57] Grimm M.O., Grimm H.S., Patzold A.J., Zinser E.G., Halonen R., Duering M., et al., Regulation of cholesterol and sphingomyelin metabolism by amyloid-beta and presenilin, Nat. Cell Biol., 2005, 7, 1118-1123

[58] Blalock E.M., Geddes J.W., Chen K.C., Porter N.M., Markesbery W.R., Landfield P.W., Incipient Alzheimer's disease: microarray correlation analyses reveal major transcriptional and tumor suppressor responses, Proc. Natl. Acad. Sci. U. S. A, 2004, 101, 2173-2178

[59] Haughey N.J., Bandaru V.V., Bae M., Mattson M.P., Roles for dysfunctional sphingolipid metabolism in Alzheimer's disease neuropathogenesis, Biochim. Biophys. Acta, 2010, 1801, 878-886

[60] Harris B., Pereira I., Parkin E., Targeting ADAM10 to lipid rafts in neuroblastoma SH-SY5Y cells impairs amyloidogenic processing of the amyloid precursor protein, Brain Res., 2009, 1296, 203-215

[61] Chi E.Y., Ege C., Winans A., Majewski J., Wu G., Kjaer K., et al., Lipid membrane templates the ordering and induces the fibrillogenesis of Alzheimer's disease amyloid-beta peptide, Proteins, 2008, 72, 1-24

[62] Yanagisawa K., Ihara Y., GM1 ganglioside-bound amyloid beta-protein in Alzheimer's disease brain, Neurobiol. Aging, 1998, 19, S65-S67

[63] Kakio A., Nishimoto S.I., Yanagisawa K., Kozutsumi Y., Matsuzaki K., Cholesterol-dependent formation of GM1 ganglioside-bound amyloid beta-protein, an endogenous seed for Alzheimer amyloid, J. Biol. Chem., 2001, 276, 24985-24990

[64] Matsuzaki K., Kato K., Yanagisawa K., Abeta polymerization through interaction with membrane gangliosides, Biochim. Biophys. Acta, 2010, 1801, 868-877

[65] Molander-Melin M., Blennow K., Bogdanovic N., Dellheden B., Mansson J.E., Fredman P., Structural membrane alterations in Alzheimer brains found to be associated with regional disease development; increased density of gangliosides GM1 and GM2 and loss of cholesterol in detergent-resistant membrane domains, J. Neurochem., 2005, 92, 171-182

[66] Stahelin R.V., Lipid binding domains: more than simple lipid effectors, J. Lipid Res., 2009, 50 Suppl, S299-S304

[67] Swartz K.J., Sensing voltage across lipid membranes, Nature, 2008, 456, 891-897

[68] Darios F., Wasser C., Shakirzyanova A., Giniatullin A., Goodman K., Munoz-Bravo J.L., et al., Sphingosine facilitates SNARE complex assembly and activates synaptic vesicle exocytosis, Neuron, 2009, 62, 683-694

[69] Wang X.Q., Sun P., Paller A.S., Ganglioside GM3 inhibits matrix metalloproteinase-9 activation and disrupts its association with integrin, J. Biol. Chem., 2003, 278, 25591-25599

[70] Yowler B.C., Schengrund C.L., Glycosphingolipids-sweets for botulinum neurotoxin, Glycoconj. J., 2004, 21, 287-293

[71] Berry-Kravis E., Dawson G., Possible role of gangliosides in regulating an adenylate cyclase-linked 5-hydroxytryptamine (5-HT1) receptor, J. Neurochem., 1985, 45, 1739-1747

[72] Fukumoto S., Mutoh T., Hasegawa T., Miyazaki H., Okada M., Goto G., et al., GD3 synthase gene expression in PC12 cells results in the continuous activation of TrkA and ERK1/2 and enhanced proliferation, J. Biol. Chem., 2000, 275, 5832-5838

[73] Fang Y., Wu G., Xie X., Lu Z.H., Ledeen R.W., Endogenous GM1 ganglioside of the plasma membrane promotes neuritogenesis by two mechanisms, Neurochem. Res., 2000, 25, 931-940

[74] Simon B.M., Malisan F., Testi R., Nicotera P., Leist M., Disialoganglioside GD3 is released by microglia and induces oligodendrocyte apoptosis, Cell Death. Differ., 2002, 9, 758-767

[75] Itoh M., Fukumoto,S., Iwamoto,T., Mizuno,A., Rokutanda,A., Ishida,H.K., Kiso,M., Furukawa,K., Specificity of carbohydrate structures of gangliosides in the activity to regenerate the rat axotomized hypoglossal nerve, Glycobiology, 2001, 11, 125-130

[76] Svennerholm L., Chromatographic separation of human brain gangliosides, J. Neurochem., 1963, 10, 613-623