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Gangliosides as a Double-Edged Sword in Neurodegenerative Disease

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1. Introduction

Gangliosides are sialic acid-containing glycolipids that are mainly localized in the outer leaflet of the plasma membrane of vertebrate cells and are involved in diverse physiological functions such as cell growth, differentiation, and cell-cell recognition (Hakomori, 1990). In the nervous system, gangliosides are highly expressed in neurons and are implicated in neurite outgrowth, synaptogenesis, and modulation of synaptic transmission (Posse de Chaves and Sipione, 2010). In this context, gangliosides have been proposed to act as co-receptors for growth factors (e.g. fibroblast growth factor) and neurotransmitters (e.g. serotonin) (Posse de Chaves and Sipione, 2010). Gangliosides are also localized in some glial cells in both gray and white matter, thereby affecting myelin sheath stability through association with myelin-associated glycoprotein (Schnaar, 2010).

There is immense large body of knowledge on the biosynthesis and catabolism of gangliosides. In brief, gangliosides are synthesized by sequential addition of single sugars catalyzed by multiple glycosyltransferases (Fig. 1). The profiles of ganglioside components in neurons and glia are developmentally regulated (Yamamoto et al., 1996; Yu et al., 2009). For instance, the dominant pathway in neurons during the neonate stage is pathway "a", which starts from GM3 and leads to GT1a via GM1 and GD1a. In adult human brain, four gangliosides (GM1, GD1a, GD1b and GT1b) are mainly produced, and these make up the majority (> 66 %) of gangliosides in the brain (Ando et al., 1978). It is also believed that each ganglioside has a specific function in the brain and is not merely an intermediate metabolite in the synthesis of more prevalent gangliosides (Yamamoto et al., 1996; Yu et al., 2009).

Gangliosides are in turn degraded by various lysosomal hydrolases with the aid of sphingolipid activator proteins. If a specific hydrolase required for this process is partially or totally missing due to a genetic deficit, gangliosides accumulate in the lysosomes and result in lysosomal dysfunction, which manifests as a lysosomal storage disease (LSD) (Jalanko and Braulke, 2009; Vitner et al., 2010). Furthermore, it has been shown that gangliosides are secondarily upregulated in many other sphingolipidoses (Vitner et al.,

2010). In this review, we do not describe the details of LSDs, but we refer to the linkage of LSDs and neurodegenerative diseases in a later section.

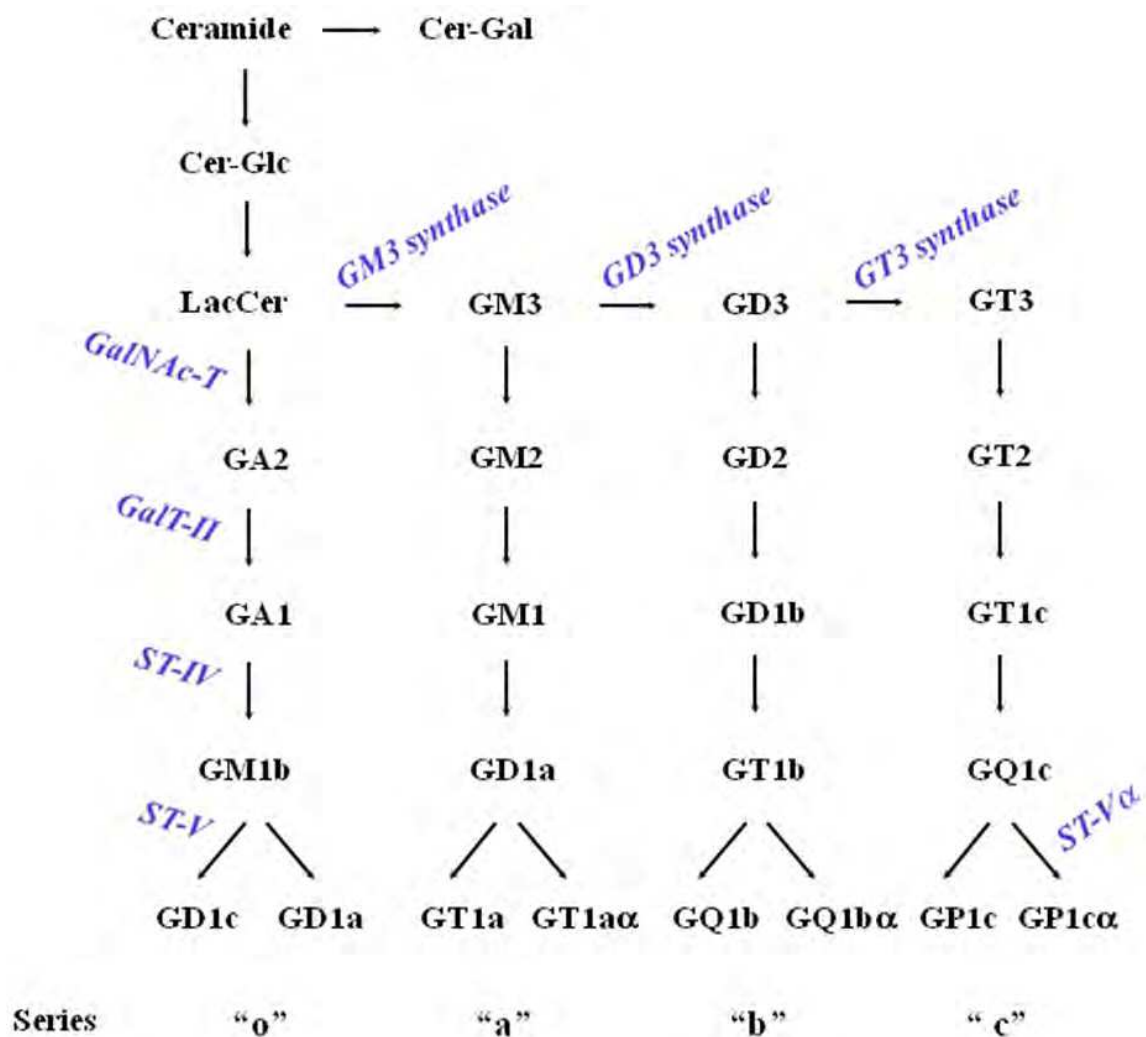


Fig. 1. Schemes of ganglioside synthesis

Synthesis is depicted starting with lactosylceramide (LacCer). GalNAc-T, GA2/GM2/GD2/GT2 synthase; GalT-II, GA1/GM1/GD1b/GT1c synthase; ST-IV, GM1b/GD1a/GT1b/GQ1c synthase; ST-V, GD1c/GT1a/GQ1b/GP1c synthase; ST-V α , GD1a/GT1a α /GQ1b α /GP1c α synthase.

Beyond LSDs, gangliosides have been implicated in various pathologies. In particular, evidence has accumulated to suggest a role of gangliosides in age-associated neurodegenerative diseases such as Alzheimer's disease (AD) and Parkinson's disease (PD). To date, the effect of gangliosides on the pathogenesis of AD is a controversial issue. Many studies suggest that gangliosides stimulate fibrillogenesis of amyloid β -protein ($A\beta$) in the early stage of pathogenesis (Yanagisawa et al., 1995), whereas others have shown that GM1 ganglioside has a beneficial effect on early onset AD, presumably through the sequestration of $A\beta$ (Matsuoka et al., 2003; Svennerholm, 1994). A limited number of reports also suggest that gangliosides are protective against the pathogenesis of PD (Hadjiconstantinou et al., 1986; Wei et al., 2009b). With this background, the main objective of this review is to outline

what is known about the roles of gangliosides in neurodegenerative diseases, including AD and PD. We also examine the linkage of these neurodegenerative diseases to LSDs.

2. Gangliosides stimulate amyloidogenesis in AD

2.1 Aggregation of A β in AD

AD is a progressive degenerative disease of the brain with loss of memory and cognition, and is characterized by the two neuropathological hallmarks of senile plaques and neurofibrillary tangles. The former are mainly composed of aggregated A β derived from amyloid precursor protein (APP), while the latter consist of paired helical filaments containing hyperphosphorylated tau (Yankner, 2000).

It is well characterized that amyloidogenic A β is generated by the consecutive cleavage of two proteases: β - and γ -secretase (Selkoe, 2008). Consistent with biochemical studies demonstrating that A β 42 is more amyloidogenic compared to A β 40 and other A β forms, it has been shown genetically that increased A β 42 production is associated with inherited familial AD. In contrast, alternative cleavage of A β at amino acid 17 by α -secretase releases sAPP α and excludes production of A β . The predominant cleavage product is sAPP α , serving to prevent production of A β .

The mechanism of neurotoxicity caused by A β is incompletely understood. However, it is generally believed that aggregation of A β results in formation of neurotoxic protofibrils and deposition of amyloid plaques (Yankner, 2000). Thus, factors regulating A β aggregation and secretion are very important for the etiology of AD.

2.2 Ganglioside interactions with A β

Considerable attention has been focused on the roles of gangliosides in the development of AD, since a number of *in vitro* studies have shown that GM1 ganglioside has a high affinity for A β and accelerates A β assembly, which leads to amyloid fibril formation. In this regard, Yanagisawa and Ihara reported that A β adopts an altered conformation through binding to GM1 in brain, which subsequently facilitates the assembly of soluble A β by acting as an endogenous seed, GA β (GM1-A β) (Fig. 2A) (Yanagisawa et al., 1995). Subsequently, Yanagisawa and colleagues developed a monoclonal antibody against purified GA β from AD brain (Hayashi et al., 2004). Notably, the antibody inhibits A β assembly *in vitro* through binding to GA β and A β . In addition, this antibody potently inhibits the assembly of A β 40 and A β 42 *in vitro*. Furthermore, peripheral administration of Fab fragments of the antibody to transgenic mice expressing a mutant APP resulted in marked suppression of A β deposition in the brain (Yamamoto et al., 2005b), thus suggesting that targeting of the endogenous seed could be a therapeutic strategy. Similar results have been obtained by other groups (Ariga et al., 2008; Choo-Smith et al., 1997; Matsuzaki and Horikiri, 1999; McLaurin and Chakrabarty, 1996).

It is of particular interest that several A β mutations in familial AD and hereditary cerebral amyloid angiopathy show distinct ganglioside affinity (Fig. 3A). A β with the Arctic-type mutation (E22G) rapidly assembles in the presence of GM1, similarly to wild type A β (Yamamoto et al., 2007). In contrast, A β with the Dutch-type mutation (E22Q) assembles in the presence GM2 or GM3 (Yamamoto et al., 2005a), and A β with the Flemish-type mutation (A21G) assembles in the presence GD3 (Yamamoto et al., 2005a). The pathological meaning of these phenomena is unknown.

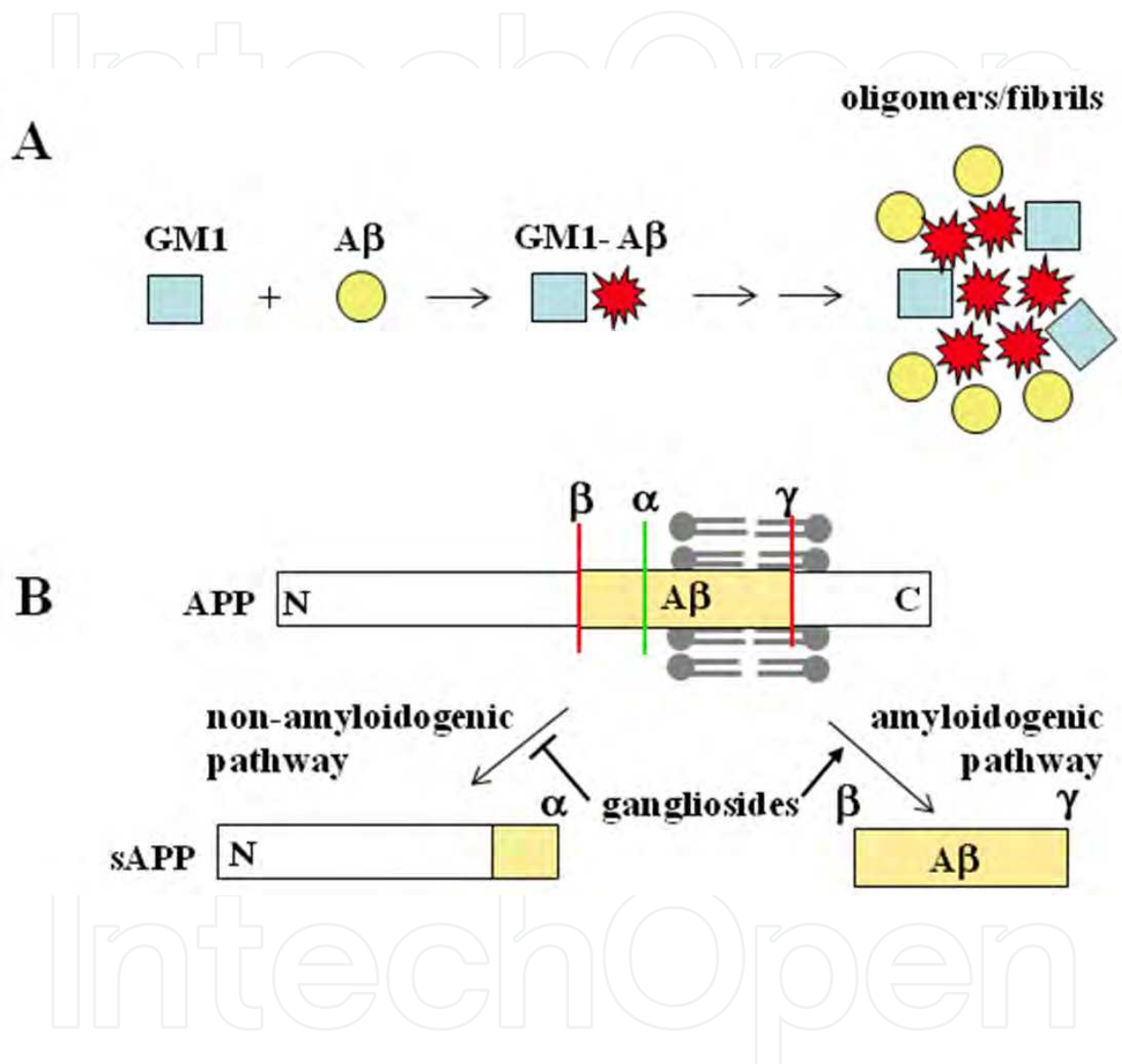


Fig. 2. Mechanism of the stimulatory effects of GM1 on A β aggregation.

A) A β adopts an altered conformation through binding to GM1, which subsequently facilitates the assembly of soluble A β by acting as an endogenous seed, GA β (GM1-A β), leading to amyloid fibril formation.

B) GM1 regulates the processing of APP by inhibition of α -secretase and stimulation of β - and/or γ -secretase activity, leading to increased secretion of A β .

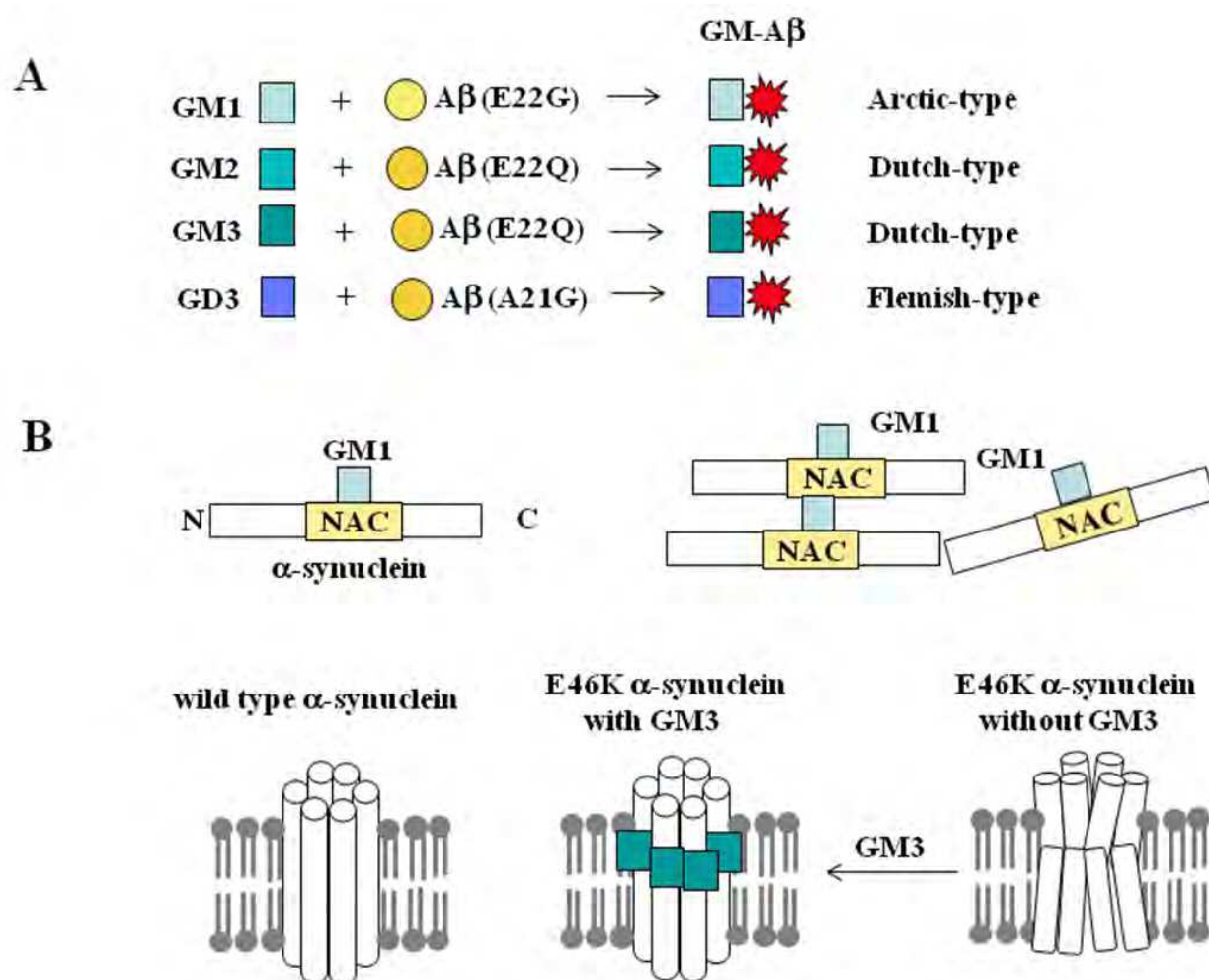


Fig. 3. Affinity of gangliosides to amyloidogenic proteins.

A) GM1, GM2/GM3 and GD3 stimulates assembly of E22G (Arctic-type mutation), E22Q (Dutch-type mutation) and A21G (Flemish-type mutation), respectively.

B) GM1 strongly inhibits α -synuclein fibrillation through binding to the NAC region, while channel formation by the DLB-linked E46K mutant of α -synuclein is corrected by GM3.

2.3 Regulatory roles of gangliosides on APP processing

Besides a direct interaction with A β , gangliosides might also dysregulate APP processing associated with increased secretion of A β , which could ultimately lead to enhanced aggregation of A β (Fig. 2B). In support of this view, exogenous addition of GM1 in cultured neurons enhances A β production in parallel with inhibition of sAPP α secretion (Zha et al., 2004). These results suggest that GM1 regulates processing of APP by regulating the activity of secretases. There are two potential mechanisms for the inhibition of α -secretase cleavage by GM1 (Zha et al., 2004). First, stiffening of the membrane due to GM1 loading may decrease sAPP α by inhibiting lateral movement and preventing the required contact between the enzyme and substrate. Second, since GM1 has been reported to have an inhibitory action on PKC, and sAPP α is positively regulated by PKC activation, GM1 may inhibit sAPP α secretion by inhibiting PKC activity. Both hypotheses require examination in further experimental work.

It is also possible that GM1 could increase β - and/or γ -secretase activity directly or indirectly. Indeed, since these secretases are thought to be localized to rafts, there might be as yet unknown biological functions underlying the connection between gangliosides and the secretases. Such a view may fit with a recent suggestion that amyloidogenic processing of APP depends on lipid rafts (Vetrivel and Thinakaran, 2010). Rafts are lateral assemblies of sphingolipids and cholesterol within the membrane. In this context, both gangliosides and cholesterol have been shown to bind to A β and facilitate amyloid fibril formation (Kakio, 2001). Taken together, these results suggest that processing of APP and generation of A β can be modulated depending on the cellular content of gangliosides.

2.4 Gangliosides and tau

Currently, only a few reports have suggested a role of gangliosides in tau aggregation and NFT formation. McGeer and co-workers showed that the monoclonal antibody A2B5, which recognizes neuronal surface gangliosides, was strongly immunopositive for many NFTs, neuropil threads, and dystrophic neurites in AD (Tooyama et al., 1992). Similar strong immunoreactivities were observed in globose-type NFTs in cases of progressive supranuclear palsy cases and in Pick bodies in Pick's disease (Yasuhara et al., 1995). Takahashi et al. showed that fetal antigens such as the C-series gangliosides and microtubule-associated protein 5 immunostained dystrophic neurites of senile plaques, NFTs and neuropil threads in the cerebral cortex in AD brain, with similar immunostaining patterns to those of tau (Takahashi et al., 1991). These results suggest that regeneration or sprouting of neurons is ongoing in association with the re-induction of gene expression characteristics in the AD brain in the early stage of development. Further studies are required to investigate the interesting possibility that gangliosides bind with tau, and that this leads to formation of NFTs and other histopathologies in AD.

2.5 Glial activation by gangliosides

It has been well characterized that gangliosides are involved in regulation of glial activation (Cammer and Zhang, 1996). In this context, recent clinical reports show that reactive astrocytes have ganglioside GD3, unlike protoplasmic astrocytes, in patients with Creutzfeldt-Jakob disease and cerebral infarction (Kawai et al., 1999). Thus, it is likely that expression and localization of individual ganglioside subtypes in neurons and glia might change under the neurodegenerative conditions of AD and PD.

3. Amelioration of the neuropathology of AD by gangliosides

As described above, many studies have shown a role for gangliosides as stimulators of A β amyloidogenesis in the early stage of AD. However, some studies have focused on the beneficial effects of gangliosides in treatment of AD. Svennerholm and Gottfries showed that the ganglioside content is reduced in early-onset or familial AD to 58-70% of that of control brains in gray matter and to 81% in frontal white matter (Svennerholm and Gottfries, 1994). Notably, both GT1b and GQ1b were significantly decreased, while GD3 was increased, suggesting that metabolism of gangliosides may be dysregulated in AD. Furthermore, given the neurotrophic activities of gangliosides (Fusco et al., 1993), it seems likely that loss of gangliosides is correlated with the severity of AD. Based on this idea, Svennerholm performed intraventricular infusion of GM1 for AD brains and concluded that

GM1 treatment was effective for early onset AD, presumably through sequestration of A β by GM1 (Svennerholm, 1994). More recently, Matsuoka et al. found that PS/APP mice administered peripherally with gelsolin or GM1 showed a substantial decrease in aggregated A β 40 and A β 42 in the brain. The result is reminiscent of the “sink effect” leading to reduction of A β accumulation in the brain following passive immunization with anti-A β antibodies (DeMattos et al., 2002). Based on this result, a novel therapeutic strategy was proposed using derivatives that are structurally related to gangliosides for specific targeting of pathogenic peptides in the periphery.

4. Roles of gangliosides in the pathogenesis of PD and related disorders

4.1 Synucleinopathies

PD is a progressive degenerative disorder of dopaminergic neurons in the substantia nigra. PD manifests clinically as movement disorder, including tremor, rigidity, and gait disturbance, while non-motor type symptoms such as cognitive difficulties and sleep problems may arise in advanced stages (Hashimoto and Masliah, 1999; Trojanowski et al., 1998). Because the pathology of PD is characterized by accumulation of α -synuclein into inclusions called Lewy bodies in neurons, the disease is classified as a synucleinopathy. This spectrum of diseases also includes dementia with Lewy bodies (DLB), multiple system atrophy, and neurodegeneration with brain iron accumulation type I (Hashimoto and Masliah, 1999; Trojanowski et al., 1998).

α -Synuclein is a presynaptic protein of unknown function that is characterized by a natively unfolded structure, with highly conserved N-termini and divergent C-terminal acidic regions in the synuclein family of peptides, which has two other members: β - and γ -synuclein (Hashimoto and Masliah, 1999). Importantly, α -synuclein is distinct from other members of the synuclein family in that it possesses a highly hydrophobic central region that has been identified as a non-amyloid β component in Alzheimer disease (Ueda et al., 1993). Since the discovery of the linkage of two missense mutations (A53T and A30P) to familial PD (Kruger et al., 1998; Polymeropoulos et al., 1997), numerous histopathological studies have shown that α -synuclein fibrils are the major constituent in Lewy bodies and glial cell inclusions in synucleinopathies (Hashimoto and Masliah, 1999). Furthermore, another missense mutation, E46K, was recently identified for DLB (Zarranz et al., 2004). All the mutant proteins have a greater propensity for self-association and aggregation compared with wild-type α -synuclein, suggesting that aggregation and protofibril formation of α -synuclein has a causative role in stimulation of neurodegenerative disorders.

4.2 Gangliosides bind with α -synuclein

Among various modulators, gangliosides may be particularly important as endogenous molecules that negatively regulate α -synuclein aggregation. In this regard, Fink and colleagues investigated the interactions between various brain sphingolipids and α -synuclein and found that α -synuclein specifically bound to ganglioside GM1 (Martinez et al., 2007). Furthermore, GM1 strongly inhibited α -synuclein fibrillation, whereas total brain gangliosides, GM2, GM3, and asialo-GM1 had weak inhibitory effects on α -synuclein fibrillation and induced some α -helical structure (Martinez et al., 2007). Given the immunoreactivity of α -synuclein in rafts, it is possible that α -synuclein is recruited by GM1

to lipid raft regions in presynaptic membranes. In this context, perturbation of GM1/raft association could induce changes in α -synuclein that contribute to the pathogenesis of PD. It is also noteworthy that GM3 may have a protective effect against channelopathy caused by α -synuclein (Lashuel et al., 2002). The ability of α -synuclein oligomers to form ionic channels was postulated as a channelopathy mechanism in human brain. Di Pasquale et al. identified a ganglioside-binding domain in the N-terminal region of α -synuclein (aa 34-50) and showed that altered ion channel formation by the DLB-linked E46K mutant of α -synuclein was corrected by GM3, but not by GM1 ganglioside (Di Pasquale et al., 2010). This result suggests that GM3, a minor brain ganglioside that is increasingly expressed with aging, might play a critical role in the neurotoxicity of α -synuclein. It is also an intriguing possibility that gangliosides might have affinity for α -synuclein mutations, as is the case for A β mutations (Fig. 3B).

4.3 Protective effects of gangliosides on lysosomal pathology of synucleinopathies

Results in cell-free systems indicate that gangliosides may protect against synucleinopathies, and we have shown that changes in endogenous ganglioside levels affect lysosomal pathology in a cellular model of synucleinopathy (Wei et al., 2009a; Wei et al., 2007). In this work, DLB-linked P123H β -synuclein neuroblastoma cells transfected with α -synuclein were used as a model system because these cells have extensive formation of lysosomal inclusion bodies. Treatment of the cells with D-threo-1-phenyl-2-decanoylamino-3-morpholino-1-propanol (PDMP), an inhibitor of glycosyl ceramide synthase, resulted in various features of lysosomal pathology, including compromised lysosomal activity, enhanced lysosomal membrane permeabilization, and increased cytotoxicity (Fig. 4). Consistent with these findings, expression levels of lysosomal membrane proteins, ATP13A2 and LAMP-2, were significantly decreased, and electron microscopy demonstrated alterations in the lysosomal membrane structures. Furthermore, accumulation of P123H β -synuclein and α -synuclein was significant in PDMP-treated cells because of the suppressive effect of PDMP on the autophagy pathway. Finally, the detrimental effects of PDMP on the lysosomal pathology were significantly ameliorated by addition of gangliosides to the cultured cells. These data suggest that endogenous gangliosides have protective roles against lysosomal pathology of synucleinopathies.

4.4 Protective effects of gangliosides in an MPTP model

There are few reports on the roles of gangliosides in synucleinopathies *in vivo*, but many studies have documented the beneficial effects of GM1 in drug-induced Parkinsonian models in animals, including those induced by treatment with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and 6-hydroxydopamine (Hadjiconstantinou et al., 1986; Jonsson et al., 1984). Mitochondrial dysfunction and oxidative stress are induced by these drugs, and it is possible that such oxidative stress is mitigated by gangliosides, similarly to suppression of oxidative stress induced by α -synuclein aggregation.

Despite the protective effects of gangliosides on drug-induced Parkinsonism, clinical trials of gangliosides for treatment of PD have been suspended because of the occasional development of an acute motor neuropathy (e.g. Guillain-Barré syndrome). Therefore, new derivatives of gangliosides are required that might efficiently sequester α -synuclein without causing neuropathy and other side effects.

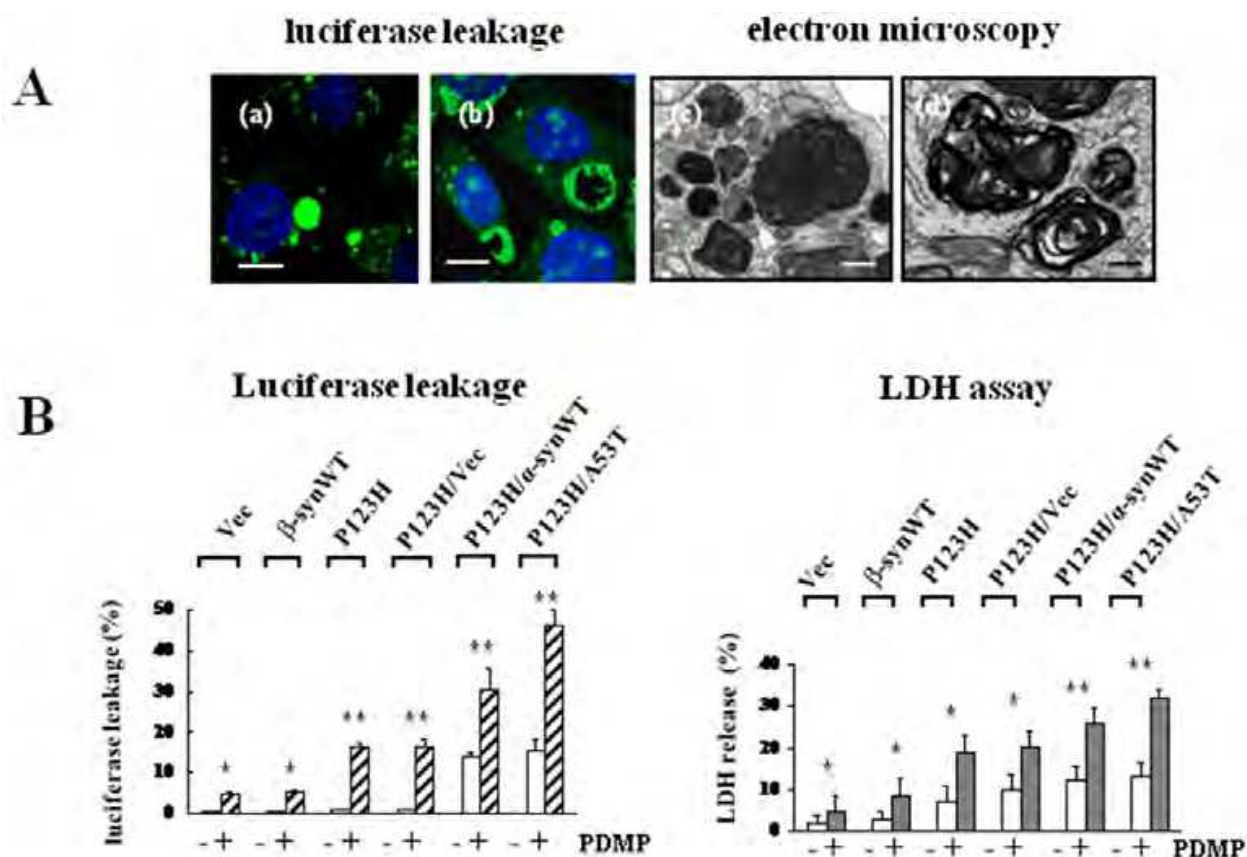


Fig. 4. Protective effects of gangliosides on lysosomal pathology in the DLB-linked cellular model.

A) Immunofluorescence showed that the fluorescence of Lucifer Yellow in P123H β -synuclein-overexpressing B103 rat neuroblastoma cells transfected with A53T α -synuclein was significantly increased by PDMP treatment (25 μ mol/L, 24 hrs) (b) compared to PDMP-untreated cells (a). Ultrastructurally, some large electron-dense inclusions were composed of various types of giant autophagosomes (c, d), the membrane integrities of which were loosened by PDMP treatment (d). Scale bars: 10 μ m (a, b) or 1 μ m (c, d)

B) Quantifications of Lucifer Yellow redistribution and LDH assay. In addition to P123H β -synuclein-overexpressing cells transfected with vector, wild-type α -synuclein, or A53T α -synuclein, vector-transfected cells, wild-type β -synuclein-overexpressing cells, and P123H β -synuclein-overexpressing cells were also analyzed. The number of Lucifer Yellow-positive cells in their cytosols at 48 hours of PDMP treatment was calculated as a percentage of the total number of cells (left panel). LDH assay was performed under the same conditions (right panel). Data are shown as means \pm SD (n = 4). *P < 0.05, **P < 0.01 versus PDMP-untreated cells. (Reprinted with permission from *Am J Pathol*, Wei et al, 2009, 174(5):1891-1909.)

5. Common pathology between neurodegenerative diseases and LSDs

5.1 LSDs are associated with Lewy bodies and NFTs

In the previous sections, we have described how gangliosides might be involved in the pathogenesis of neurodegenerative disorders such as AD and PD. Conversely, accumulating

evidence suggests that LSDs, including Gaucher disease, Sandhoff disease, Nieman-Pick C1 disease, Tay-Sachs disease, metachromatic leukodystrophy, β -galactosialidosis, and adrenoleukodystrophy, are associated with neuropathologies such as Lewy bodies and NFT (Saito et al., 2004; Suzuki et al., 2003; Suzuki et al., 2007). Furthermore, a recent study suggested that LSDs and neurodegenerative diseases are characterized by disorder of the autophagy-lysosomal pathway (Settembre et al., 2008; Tamboli et al., 2011). The overlapping pathology between the two disease spectrums might be attributable to direct and/or indirect interactions of gangliosides with amyloidogenic proteins, including $A\beta$ and α -synuclein. However, the two disease types are currently treated as completely separate entities, which may mainly be due to the differences in onset age and clinical symptoms.

5.2 Genetic link between neurodegenerative diseases and LSDs

Emerging genetic evidence suggests that the distinction between the two disease types should be reconsidered. In this regard, several cohort studies of screening for the glucocerebrosidase gene in patients with PD and DLB have identified a high frequency of mutations (Hruska et al., 2006; Mitsui et al., 2009; Sidransky, 2004), suggesting that mutation of this gene is a risk factor for α -synucleinopathies. Furthermore, the affinity of gangliosides for amyloidogenic proteins raises the intriguing possibility that the two disease spectrums are linked to each other more closely than previously thought. GM1 associates with the β -sheet structure of α -synuclein (probably with the central NAC region), while GM3 preferentially binds to the N-terminus of α -synuclein. GM2 is abundantly accumulated in Sandhoff disease and Tay-Sachs disease, both of which have a Lewy body pathology (Suzuki et al., 2003), and this raises the question of how GM2 interacts with α -synuclein. Furthermore, other sphingolipids may have affinity for α -synuclein, given the accumulation of α -synuclein in other types of LSDs.

6. Conclusion

In summary, gangliosides may be involved in the pathogenesis of AD, either by stimulating the seeding step of amyloidogenesis or through deregulation of the processing of APP. On the other hand, addition of gangliosides may be a useful strategy to sequester $A\beta$, leading to suppression of extracellular deposits of $A\beta$. In a similar context, the sequestering effects of gangliosides on α -synuclein may protect against an α -synuclein pathology, such as channelopathy and intracellular lysosomal inclusion. Thus, currently available data suggest that gangliosides may act as a double-edged sword in neurodegenerative diseases such as AD and PD.

However, information is still limited and further studies are required to elucidate the roles of gangliosides with respect to $A\beta$ and α -synuclein, and also with tau and glial activation. Finally, the affinity of gangliosides to amyloidogenic proteins is an issue that may provide a key to solve as yet unknown mechanisms underlying common aspects of age-associated neurodegenerative diseases and LSDs.

7. Acknowledgements

This work was supported in part by a grant-in-aid for Science Research from the Ministry of Education, Culture, Sports, Science, and Technology, Japan. The authors have no conflict of interest to declare.

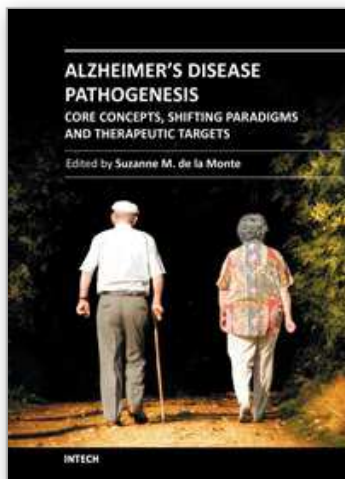
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Alzheimer's Disease Pathogenesis-Core Concepts, Shifting Paradigms and Therapeutic Targets

Edited by Dr. Suzanne De La Monte

ISBN 978-953-307-690-4

Hard cover, 686 pages

Publisher InTech

Published online 12, September, 2011

Published in print edition September, 2011

Alzheimer's Disease Pathogenesis: Core Concepts, Shifting Paradigms, and Therapeutic Targets, delivers the concepts embodied within its title. This exciting book presents the full array of theories about the causes of Alzheimer's, including fresh concepts that have gained ground among both professionals and the lay public. Acknowledged experts provide highly informative yet critical reviews of the factors that most likely contribute to Alzheimer's, including genetics, metabolic deficiencies, oxidative stress, and possibly environmental exposures. Evidence that Alzheimer's resembles a brain form of diabetes is discussed from different perspectives, ranging from disease mechanisms to therapeutics. This book is further energized by discussions of how neurotransmitter deficits, neuro-inflammation, and oxidative stress impair neuronal plasticity and contribute to Alzheimer's neurodegeneration. The diversity of topics presented in just the right depth will interest clinicians and researchers alike. This book inspires confidence that effective treatments could be developed based upon the expanding list of potential therapeutic targets.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Akio Sekigawa, Masayo Fujita, Kazunari Sekiyama, Yoshiki Takamatsu, Jianshe Wei and Makoto Hashimoto (2011). Gangliosides as a Double-Edged Sword in Neurodegenerative Disease, *Alzheimer's Disease Pathogenesis-Core Concepts, Shifting Paradigms and Therapeutic Targets*, Dr. Suzanne De La Monte (Ed.), ISBN: 978-953-307-690-4, InTech, Available from: <http://www.intechopen.com/books/alzheimer-s-disease-pathogenesis-core-concepts-shifting-paradigms-and-therapeutic-targets/gangliosides-as-a-double-edged-sword-in-neurodegenerative-disease>

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