

Chapter 19

Glycoconjugate Changes in Aging and Age-Related Diseases

Susumu Ando

Abstract The significance of glycosphingolipids and glycoproteins is discussed in their relation to normal aging and pathological aging, aging with diseases. Healthy myelin that looks stable is found to be gradually degraded and reconstructed throughout life for remodeling. An exciting finding is that myelin P0 protein is located in neurons and glycosylated in aging brains. In pathological aging, the roles of glycosphingolipids and glycoproteins as risk factors or protective agents for Alzheimer's and Parkinson's diseases are discussed. Intensive studies have been performed aiming to remove the risks from and to restore the functional deficits of the brain. Some of them are expected to be translated to therapeutic means.

Keywords Aging • Alzheimer's disease • Parkinson's disease • Ganglioside • Glycoprotein • Cholinergic • Remyelination • Sialylcholesterol • Warfarin

Abbreviations

APP	Amyloid precursor protein
A β	Amyloid beta
BBB	Blood–brain barrier
BDNF	Brain-derived neurotrophic factor
CBA	Glucocerebrosidase
CNS	Central nervous system
GnT-III	<i>N</i> -acetylglucosaminyltransferase III
LCB	Long-chain base

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MAP5	Microtubule-associated protein 5
NCAM	Neural cell adhesion molecule
NFTs	Neurofibrillary tangles
OPC	Oligodendrocyte precursor cell
PD	Parkinson's disease
P-gp	P-glycoprotein
PSA	Polysialic acid
SAP	Serum amyloid P

19.1 Preface

Aging is defined as the detrimental process of a body composed of somatic cells after cessation of reproductive activity. The body as a short-term vehicle for passing on the genes to the next generation is evolutionally disposable as based on the disposable soma theory of aging (Kirkwood 1977). The theory means that the body must take natural courses to death. Individuals, however, do not always fulfill their maximum life spans, but frequently suffer from various diseases injurious to their health. In this sense, aging is classified into two types, aging without disease, physiological aging and aging with disease, pathological aging. In this article, glycoconjugate changes in the brain that occur during physiological aging are described first, followed by discussion of their possible participation in the pathophysiology and pathogenesis of age-related neurological diseases. Kobata (2011) introduced the word “glycogerontology” for the field covering the roles of glycoconjugates in relation to gerontology and geriatrics. The physiology and pathology of glycosphingolipids (GSLs) and glycoproteins, will be reviewed here with special reference to their roles in glycogerontology.

19.2 Glycoconjugates in Aging Brains

19.2.1 Age-Related Changes of Glycosphingolipids in the Brain

GSLs are composed of neutral and acidic glycolipids, and the latter are divided into two groups, sulfatides and sialic acid-containing GSLs or gangliosides. The sialyl-oligosaccharide structures of gangliosides show great diversity as a result of the combination of neutral oligosaccharides of various chain lengths and different numbers of sialic acids attached to the core neutral sugars (Ando 1983) as shown in Fig. 19.1. Because of the complexity in their carbohydrate structure, it is hypothesized that gangliosides play crucial roles in cellular events (Cantù et al. 2011; Ohmi et al. 2012; Yu et al. 2012), and as a result they have attracted the most attention of

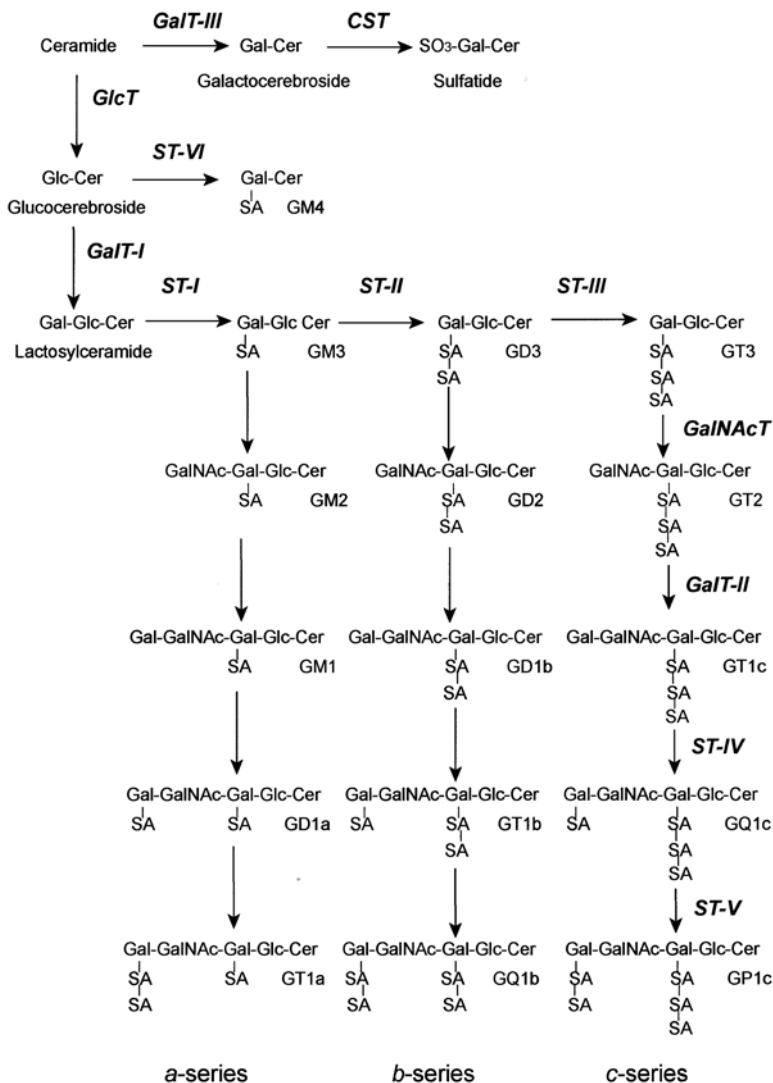


Fig. 19.1 Pathways for formation of sulfatide and gangliosides. Transferases are typed in *bold-italic*. *Cer* ceramide, *CST* galactosylceramide sulfotransferase, *Gal* galactose, *GalNAc* *N*-acetylgalactosamine, *Glc* glucose, *GalT-I* galactosyltransferase I, *GalT-II* galactosyltransferase II, *GalT-III* galactosyltransferase III, *GlcT* glucosyltransferase, *SA* sialic acid. ST-I, II, III, IV, V, and VI correspond to sialyltransferases I (GM3 synthase), II (GD3 synthase), III, IV, V, and VI, respectively

any of the GSLs from researchers in aging research. The supposition is that alterations in the concentration and composition of gangliosides in aging neural membranes should be correlated with age-related functional changes in the brain.

Age-related compositional changes of gangliosides in the human brain were first reported by (Suzuki 1965). In the frontal cortices, GD1a, which is predominant

in new-born brains, decreases with age. GM1 also tends to decrease. On the other hand, GD1b and GT1b both increase and by age 30 reach adult levels which normally remain essentially constant until a person is near 90 years of age. These trends in ganglioside pattern changes were supported by the data reported by Segler-Stahl et al. (1983). Similarly, gangliosides GD1b, GT1b, and GQ1b in *b*-series gangliosides (Fig. 19.1) were shown to increase with age, while GM1 and GD1a decrease (Svennerholm et al. 1989). As GM1 is the major component of myelin (Ledeen and Yu 1982), *b*-series gangliosides in neural components other than myelin may continue to increase to reduce the relative contents of GM1 in the brain after the period of active myelination. Alternatively, the decrease of GM1 in advanced age may indicate some disintegration of myelin structure. Disruption of the myelin sheath has been reported to occur in aged brain (Peters et al. 2001). The myelin components were shown to never be stable but to be dynamically turned over in physiological aging (Ando et al. 2003). Probably as the consequence of the remodeling of the composition of myelin, cognitive declines with aging were hypothesized to correlate with the altered white matter tracts (Aine et al. 2011; Schulze et al. 2011).

19.2.2 Age-Related Changes of Glycosphingolipids in Synapses

The brain is composed of neurons, glia, and blood vessels. The ganglioside distribution patterns were shown biochemically to be distinct for neural cell types as well as their subcellular fractions (Ando 1983). Immunohistochemical identification of the regional distribution of major gangliosides in the rat brain (Kotani et al. 1993), indicated that a specific ganglioside or set of gangliosides might be responsible for particular neuronal functions. To elucidate their biological roles, it will be important to obtain information on the ganglioside contents and composition of particular cells and subcellular components. In respect to neurons, nerve endings or synapses are functional elements for neurotransmission, and gangliosides in synaptic membranes are thought to affect efficiency of acetylcholine release (Ando 2012; Ando et al. 2004; Tanaka et al. 1997) and long-term potentiation at synapses (Furuse et al. 1998; Wieraszko and Seifert 1986). Waki et al. (1994) developed excellent methods for quantitative isolation of gangliosides from membrane preparations and for their accurate quantitation using gas chromatography–mass spectrometry. Using this method the ganglioside content and composition of mouse brain synaptic plasma membranes was shown to remain constant from adult to senescence. This result seems to be reasonable. Functional units such as synaptic plasma membranes may retain the structure required for their function until senescence, even though the density of the units decreases with age resulting in the changes in ganglioside content and composition observed in tissues or whole brains as described in Sect. 19.2.1.

During the juvenile period of brain development, the content of GD1a was shown to increase and then decrease in the human frontal cortex (Suzuki 1965). GD1a found in cerebral microsomal fractions may be considered a marker for dendritic arborization (Yusuf and Dickerson 1978). Synaptic membrane preparations from mouse brains showed high concentrations of GD1a after birth and reduced levels of GD1a at 6 months of age (Waki et al. 1994). The transient increase in GD1a seemed to coincide with the temporary increase in synaptic density in infant brains (Huttenlocher 1979), and its decrease might correspond to synapse elimination during brain development. GD1a levels then remained constant throughout adult life. These observations indicate that GD1a expression may be related to arborization and synaptogenesis that occur in the initial formation of the neuronal network.

19.2.3 Age-Related Changes in Myelin GSLs

Many studies have examined the effects of age on various brain regions. Most of them, however, were focused on specific areas and the data seemed to be too fragmented to make valid comparisons. Upon comparing results obtained for the composition of 16 automatically segmented measures of the human brain Walhovd et al. (2005) found distinct age changes in different brain structures. Two representative age responses observed were that the volume of white matter showed a curvilinear relationship with age, while the volume of gray matter was reduced in a linear fashion. In the case of cerebral white matter, the volume increased early in life, and decreased during senescence following the steady-state adult period. The main components of white matter are axons and myelin sheaths. While no changes were found in the diameters of axons with age, the numbers of myelin lamellae increased in aged monkeys (Peters et al. 2001). These morphometric observations (Peters et al. 2001; Walhovd et al. 2005) indicate that some changes may continuously take place in myelin components across one's life span.

Age-related changes in the glycosphingolipids composition of white matter were determined for the human brain (Svennerholm et al. 1994). The three major GSLs, cerebroside, sulfatide, and ganglioside were found to decrease ($\mu\text{mole per gram tissue weight}$) with advancing age starting at ~ 20 years. The same group published somewhat different age-related changes for these glycolipids in separate papers. Cerebroside content in white matter remained constant till 90 years and then sharply declined (Svennerholm et al. 1991). Another paper reported that GM1 in white matter increase in the early developmental age until 1 year and remained at a constant level in the adult (Vanier et al. 1971). These discrepancies might come from their research designs in which glycoconjugates were quantified based on fresh tissue weights. Cellular composition and even tissue water content may change with aging. To avoid such effects analyses should be performed on distinct components of the brain and GSL content related to dry weight.

Norton and Poduslo (1973) isolated myelin fractions from rat brains and found age-related changes in lipid composition along with myelination. The rate of

accumulation of cerebroside in the brain paralleled that of myelin. The content of cerebroside in myelin increased during the active myelinogenesis period till 30 days of age, and then remained at constant until rats were 425 days. On the other hand, the content of sulfatide in myelin increased more slowly than that of cerebroside even during active myelinogenesis, and continued to increase gradually during adult life. Sulfatide is produced from cerebroside by the action of galactosylceramide sulfotransferase (Fig. 19.1), and the enzyme is thought to remain active in the remodeling of mature myelin. The biological function of sulfatide was revealed using a mouse model incapable of synthesizing it (Ishibashi et al. 2002). The sulfatide-deficient mice were normal at birth, developed neurological deficits after 6 weeks of life, and survived to >1 year of age. Immunohistochemical studies indicated that sulfatide was not necessary for initial cluster formation, but was essential for proper localization of axonal proteins such as Na⁺ and K⁺ channels as well as the maintenance of these proteins around nodes.

Yu and Iqbal (1979) found that gangliosides GM1 and GM4 were concentrated in the myelin fraction isolated from the human brain. Since myelin constitutes the bulk of the oligodendrocyte plasma membranes, GM1 and GM4 may be synthesized in the cell bodies and incorporated into myelin. This leads to the question of why the ganglioside composition of myelin is quite dissimilar to that of parent oligodendrocytes whose ganglioside pattern is complex and rather similar to that of neurons. Saito and Yu (1992) performed an *in vitro* experiment in which incubation of the myelin fraction obtained from young rats with sialidase was found to produce a ganglioside pattern similar to that observed in *in vivo* maturation of myelin. They suggested that myelin-associated sialidase may play a role in the processing of gangliosides in myelin membranes. This is an interesting hypothesis in light of another suggesting a role for the sialidase-GM1 interaction in stabilization of the multilamellar structure of myelin sheaths (Saito and Yu 1993). The activities of membrane-bound sialidase were determined for synaptic plasma membranes and nuclear membranes, and their age-related changes examined. The enzyme activities decreased by one-sixth in synaptic plasma membranes (Saito et al. 1995) and by one-third in nuclear membranes (Saito et al. 2002) in old animals.

In my laboratory, the lipid composition of myelin fractions isolated from mouse brains at different ages was examined (Ando 1985). Age-related changes of cerebroside and sulfatide were a little different from those reported for rats (Norton and Poduslo 1973). Our data showed that the contents of cerebroside and sulfatide as expressed per dry weight of myelin both remained at near constant levels from weaning to old age (20–820 days of age), and increased, almost suddenly, at the oldest old age of 1,055 days. With respect to gangliosides in mouse myelin, the content continued to increase from young to old age, and suddenly decreased at the last stage of life. The changes seen in myelin GSLs at the extreme old age may indicate occurrence of an abrupt metabolic disruption in myelin. Similar age-changes in myelin glycolipids at the final stage of life were also reported for human brains (Walhovd et al. 2005; Svennerholm et al. 1991).

To understand the age-related changes in myelin composition metabolic turnover rates for myelin components were measured (Ando et al. 2003). Myelin has a tightly compacted multi-membrane structure containing the least volume of cytosole among membranes, and was not expected to be actively metabolized, so short-term labeling experiments seemed inappropriate. In long-term monitoring studies, depending upon precursors used, the turnover rates of radioisotope-labeled myelin components were reported to vary 6–167 days as half-lives for phosphatidylcholine (Sun and Sun 1979). These big discrepancies may reflect the fact that different tracers recycle at different rates. Our *in vivo* deuterium-labeling method was shown to eliminate the contribution of the recycling or reuse of labels so that more reliable turnover rates of myelin components could be determined (Ando et al. 2003). Turnover rates of myelin components as half-lives were calculated from decay curves of initially labeled molecules. In fact, very long half-lives of up to 1 year could be measured. Individual components of myelin in the mouse brain were found to be metabolized at separate rates, and their turnover rates were affected differently by aging. Turnover rates of GSLs were calculated from the incorporation rates or disappearance rates of their labeled neutral sugar moieties. Cerebroside and GM1 appeared to be rapidly incorporated into myelin in infant brains as were cholesterol and phospholipids, and their turnover rates varied with aging, decreasing during young and adult periods and rebounding in the senescence stage. The accelerated metabolism of myelin in old age may explain the curious compositional changes observed at the last stage of a mouse's life (Ando 1985) as well as in human brains (Walhovd et al. 2005; Svennerholm et al. 1991). The metabolism of GM1 appeared to be composed of two compartments in myelin, one with a short half-life of 52 days and another with a long half-life of 131 days, which correspond to rapidly and slowly exchanging pools, respectively (Ando et al. 2003). The concept that metabolic turnover of membrane components occurs continuously in mature myelin and the finding that turnover rates change with age may provide a better understanding of the mechanism underlying myelin aging.

19.2.4 Alterations in the Lipid Portions of Glycosphingolipids with Aging

GSLs are inserted into the outer layer of neural membranes through their ceramide portions. Ceramide is composed of a fatty acid linked to sphingosine via an amide linkage. It is known that the ceramide portion plays a number of biological roles. It may control the interaction of the saccharide portion with external ligands (Kannagi et al. 1982), and regulate the aggregative properties and surface dynamics of the GSLs (Yohe et al. 1976). In a model system using synaptosomes and liposomes increasing concentrations of gangliosides in the membranes were shown to increase membrane fluidity or decrease membrane microviscosity (Ando et al. 1986). Gangliosides may affect membrane physicochemical characteristics such as fluidity through the homophilic interaction of the sialylsaccharides and the heterophilic

interaction of the saccharides with other ligands, and further through the lipidic interaction of their ceramide portions with other lipids in membranes. Recently, Furukawa's group (Ohmi et al. 2012) showed, using mice expressing mutant ganglioside synthases, that glycolipid-enriched microdomain/rafts architecture was destroyed by ganglioside deficiency. Others generated mutant mice defective in their ability to synthesize ceramide containing very long-chain fatty acids (C22-C24) due to ablation of ceramide synthase 2 (Ben-David et al. 2011). The mice had reduced levels of both nonhydroxy-C22-C24- and 2-hydroxy-C22-C24-galactosylceramide, and developed brain lesions. Myelin degeneration and detachment occurred in the brain. The mice also exhibited abnormal motor behavior and histological abnormalities such as vacuolization and astrogliosis.

Age-related changes in the ceramide portion of GSLs were studied in order to learn more about the probable physiological roles of ceramides. Changes in fatty acid composition were studied using samples from human brains (Mansson et al. 1978; Svennerholm and Ställberg-Stenhagen 1968). The adult fatty acid composition of cerebrosides and sulfatides in regard to degree of unsaturation and total percentage of C22-C26 acids was reached at 2 years of age, but the percentage of odd-numbered fatty acids continued to increase up to about 10–15 years. Fatty acid changes occurred in cerebrosides first and in sulfatides later. The delay in sulfatides may reflect the fact that cerebrosides are precursors in the synthesis of sulfatides (Norton and Poduslo 1973). Stearic acid was reported to be the major component in the ceramide portions of gangliosides in human brains (Mansson et al. 1978). The proportion of stearic acid was found to decrease from about 94 to 86 % in both GM1 from white matter and GT1 from the cerebral cortex upon aging. These data were obtained from studies of three brains, one from a 77 year old (Svennerholm and Ställberg-Stenhagen 1968), one from a 71 year old and one from an 89 year old (Mansson et al. 1978).

Long-chain bases (LCBs) or sphingosines in the ceramide portion of GSLs in the brain are composed of two major species, d18:1 and d20:1. The compositional changes in LCB with aging were first observed in human brains (Mansson et al. 1978). The averaged values for the molar proportion of d20:1 were shown to increase from about 20 to 70 % with advancing age. Age-related changes in the LCBs of gangliosides were studied in detail using rat forebrains (Palestini et al. 1990). The d18:1 LCB, predominant at 3 days (91–96 %), diminished with age and at 2 years was 73, 65, 61, 59, and 45 % of the total for GD1a, GM1, GT1b, GD1b, and GQ1b, respectively. The content of d20:1 LCB, low at birth (4–9 %), increased with age in all gangliosides and at 2 years 27–55 % of the total. Molecular species of all gangliosides carrying d18:1 LCB were virtually devoid of C20 fatty acid. Analysis of the ceramide portions of gangliosides isolated from synaptosomes and myelin fractions of rat brains of different ages indicated that the fatty acid composition did not undergo appreciable changes (Palestini et al. 1993). Large age-related changes in LCB composition were observed in all gangliosides in both synaptosomal and myelin fractions. The steady increase in the proportion of d20:1 LCB observed in the two subcellular fractions appeared to coincide with the age-related changes reported for gangliosides isolated from rat whole brains.

Sugiura et al. (2008) provided a good answer for the question of whether the different molecular species would show different distribution patterns in the brain. Using imaging mass spectrometry, they found that gangliosides containing d18:1 or d20:1 LCB were differentially distributed in mouse brain. While the d18:1-species was widely distributed throughout the frontal brain, the d20:1-species selectively localized along the entorhinal-hippocampal projections, especially in the molecular layer of the dentate gyrus. The finding of developmental- and age-related accumulation of the d20:1 species in the hippocampal formation provided evidence that changes in the ganglioside molecular species may contribute to the process of brain aging.

19.2.5 Age-Related Changes in the Carbohydrate Structure of Glycoproteins

The glycan moieties of glycoproteins are known to play crucial roles not only in modulating the property of the stem glycoproteins, but also in regulating various molecular recognition processes (Kobata 1992). In the developing brain, nervous system glycans have been implicated as important mediators of adhesive interactions among neural cells (Schachner and Martini 1995). Age-related changes in glycoproteins in the central nervous system (CNS) have been infrequently documented in the literature, but evidence for them has been summarized in review articles (Kobata 2011; Sato and Endo 2010). The myelin glycoprotein P0 is one that has been studied.

Originally using a goat anti-P0 antibody and immunofluorescence, the myelin P0 glycoprotein was found to be located exclusively in the myelin of peripheral nerves, but not in CNS myelin (Ishaque et al. 1980). Subsequently, Endo's group (Sato et al. 1999) was able to show that P0 was present in the spinal cord of the rat. They further demonstrated by immunohistochemical and immunocytochemical analyses that CNS neuronal cells expressed P0 (Sato and Endo 2000). To explore whether any age-related changes occurred in the glycans of CNS P0, glycoproteins obtained from the brain or spinal cord of 9-week old and 29-month old rats were separated by electrophoresis and stained with *Lens culinaris* agglutinin (Sato et al. 1999). This lectin specifically binds to the P0 glycan. While the glycoprotein patterns of spinal cords showed marked differences between the two age groups, samples from brains did not. Nonglycosylated P0 molecules present in the young spinal cord were replaced with glycosylated ones during aging. As it was reported that the glycan moiety of P0 plays an important role in cell-cell adhesion (Yazaki et al. 1992), the appearance of glycosylated P0 may function in the remodeling of neural structures that occurs with aging. A study on age-related changes in the glycan structure of peripheral nerve myelin glycoprotein P0 indicated that P0 from adult rats contained high-mannose and/or hybrid-type oligosaccharides not seen in P0 from 5-day-old nerves (Brunden 1992).

Following the finding of expression of P0 in the mammalian CNS, its cellular localization in rat spinal cord was examined by immunohistochemical and

immunocytochemical methods using a polyclonal anti-P0 antibody (Sato and Endo 2000). Nissl staining-positive motor neurons and sensory neurons showed strong reactivity with the antibody. The neuronal localization of P0 was confirmed by double immunofluorescence labeling using the anti-P0 antibody and an anti-neurofilament monoclonal antibody. Further analysis indicated that neurons expressing P0 in the spinal cord of 30 month-old rats had a different morphology than those of 14 week-old rats. The number of neurons stained in the old rats was about 80 % of that in the young rats, while the average size of neurons in the old rats was about 62 % of that in young rats. These observations indicate that both cell number and average size of neurons in the spinal cord decreased with age supporting the hypothesis that the activity and survival of the neurons might be regulated or changed by age-related changes in glycosylation of P0.

Endo's lab (Sato et al. 2006), using 2D-electrophoresis using Concanavalin A staining, surveyed the contents of cytosolic glycoproteins in rat cerebral cortices and found several spots increased in the aged brains. The glycoprotein that was most prominently increased was identified as cathepsin D. It was detected in the cytosolic fractions of aged rats, but not in those of young adult rats. Cathepsin D in the microsomal fractions did not show age-related changes. The increase of cytosolic cathepsin D during aging was not due to disruption of the lysosomal membrane, because other lysosomal enzymes did not increase in the cytosolic fractions. The level of cathepsin D transcripts in aged rats was 1.6 times higher than in the young adults. Cathepsin D is known to digest neurofilaments and tau (Bednarski and Lynch 1996) which are components of the cytoskeleton of neuronal cells. The enhanced expression of cathepsin D may facilitate cytoskeletal degradation leading to morphological changes and functional loss of neurons in aged brains.

Sialic acid is present in both glycoproteins and gangliosides. It attaches to the nonreducing terminals of sugar chains by α 2-3, α 2-6, or α 2-8 ketosidic linkage. A homopolymer of α 2-8-linked sialic acid moieties (polysialic acid, PSA) is found on neural cell adhesion molecules (NCAM), and is known to modulate the adhesion property of NCAM and to regulate neurite outgrowth and cell migration (Brusés and Rutishauser 1998). PSA-NCAM (embryonic form of NCAM) was shown to be present in adult brain regions where neuronal regeneration occurred but its expression decreased during aging (Seki and Arai 1991). PSA-NCAM expression is lost after the cessation of neuronal cell migration and synapse formation, but can be retained by axons capable of synaptic remodeling.

The histochemical distribution of sialyl α 2-3 galactose and sialyl α 2-6 galactose was examined in the rat hippocampus using *Maackia amurensis* lectin to label the former, and *Sambucus sieboldiana* for the latter, and electron microscopy to visualize them (Sato et al. 2001). Both lectins stained the plasma membranes of pyramidal cells and synapses. The staining intensity by both the lectins of synapses was reduced in 30-month-old rats. In addition to staining glycoproteins, the *Maackia amurensis* lectin could also bind all of the series of gangliosides possessing sialyl α 2-3 galactose linkages. The *Sambucus sieboldiana* lectin could bind the α -series of gangliosides possessing sialyl α 2-6 galactose. Expression of sialyl α 2-6 galactose decreased in the aged brain.

19.3 Glycoconjugates and Age-Related Diseases

19.3.1 *Gangliosides and the Pathology of Alzheimer's Disease*

An interesting question addressed by Mizutani's group was whether the histopathological changes that occur in Alzheimer's brains were the results of accelerated aging (Mizutani and Kasahara 1997; Yamada et al. 1998). In advancing physiological or normal aging, morphometric measurements of brain volumes in comparison with intracranial volumes showed a very slow progression of brain atrophy and an insignificant correlation between the rate of atrophy and age. In contrast, similar measurements with Alzheimer's brains revealed intensive atrophy occurred (Yamada et al. 1998). The hippocampal atrophy observed in Alzheimer's brains was distinct from that seen in control, nondemented brains (Mizutani and Kasahara 1997). In the hippocampal formation of control brains, no atrophy was observed in the hippocampus and parahippocampus. In fact, in all cases with Alzheimer's disease the stratum lacunosum-radiatum was decreased in thickness, and this was accompanied by loss of myelin and fibrillary gliosis. Interestingly, the numbers of senile plaques and neurofibrillary tangles (NFTs) and the degrees of neuronal loss in the pyramidal layer varied from case to case. The severer degeneration in the parahippocampus including the entorhinal cortex than in the hippocampus indicates that degeneration of the entorhinal cortex may induce degeneration of the hippocampus because the perforant pathway in the hippocampus originates from the entorhinal cortex. Entorhinal cortex dysfunction was detected in early Alzheimer's disease by positron emission tomography (Eustache et al. 2001). In regard to cognitive dysfunction, the concept of "synaptic pathology," in which synaptic loss is the major correlate of cognitive deficits, was proposed by Terry et al. (1991; Masliah and Terry 1993), and supported by others (Blennow et al. 1996; Heinonen et al. 1995; Scheff et al. 1993). Based on the observations made using Alzheimer's brains, a dementia animal model was successfully generated by inducing synapse-specific lesions in the entorhinal cortex (Ando et al. 2002). This supported the synaptic pathology hypothesis.

Alzheimer's disease is an age-related disorder, but is not the result of advanced normal aging. The progressive cognitive dysfunction seen in Alzheimer's disease is characterized by the accumulation of senile plaques and NFTs, and the degeneration of neurons in brain regions such as the hippocampal formation. A recent review of the literature on the correlation of Alzheimer's neuropathologic changes with cognitive status stresses that the severity of cognitive impairment correlates best with the burden of neocortical NFTs (Nelson et al. 2012). NFTs are related to neuronal loss. In contrast, from the standpoint of the pathogenesis of Alzheimer's disease, generation of amyloid β ($A\beta$)-peptides is thought to be at the beginning of a cascade that leads to the disease. Recent studies indicate that assembly of $A\beta$ -peptides into $A\beta$ -oligomers or protofibrils, can cause cognitive declines by disrupting synaptic function (Dahlgren et al. 2002; Matsumura et al. 2011; O'Nuallian et al. 2010). Wild type $A\beta$ monomers assemble first into protofibrils and then amyloid fibrils to form

senile plaques. A β -peptides deposit in diffuse plaques, the earliest stage of senile plaques. Yanagisawa et al. (1995) isolated the diffuse plaque fraction as a “light A β ” from Alzheimer’s disease and Down’s syndrome brains and found that A β associated with diffuse plaques bound to ganglioside GM1 in a noncovalent fashion. Yanagisawa’s group hypothesized that GM1-bound A β acted as a seed in the initiation of amyloid fibril formation (Kakio et al. 2001). Another in vitro experiment showed that A β selectively bound to membranes containing GM1 and that no A β binding was observed with GM1-free membranes (Choo-Smith et al. 1997). Studies of brains from monkeys indicated that GM1-A β was formed in early endosomes and transported to late endosomes for degradation (Kimura and Yanagisawa 2007). It is thought that impaired recycling in the endosome pathway results in accumulation of GM1-A β in endosomes and that its subsequent transport to the cell surface where it acts as a seed for amyloid fibril formation. Furthermore, it was shown that a toxic soluble A β assembly was formed in a GM1 dependent manner through incubation of soluble A β with neuronal membranes prepared from aged mouse brains (Yamamoto et al. 2007). These observations may help to define the mechanism underlying the plaque-independent neuronal death seen in Alzheimer’s disease.

19.3.2 Expression of Unusual Gangliosides in the Alzheimer’s Brain Indicative of Brain Plasticity

Expression of *c*-series gangliosides in Alzheimer’s brains was reported by our laboratory (Takahashi et al. 1991). Since the *c*-series of gangliosides with trisialyl residues were structurally identified (Ando and Yu 1979), the metabolic pathway for their synthesis from GT3 (Fig. 19.1) was established (Yu et al. 2004). The *c*-series gangliosides were found to be expressed in embryonic brains and designated as fetal antigens (Hirabayashi et al. 1988). Anti-*c*-series ganglioside antibodies were found to label neuritic elements composing senile plaques as well as perivascular amyloid deposits (Takahashi et al. 1991). Positive staining with the antibodies was not observed in brains of nondemented individuals, except for those containing a small number of senile plaques. NFTs were immunolabeled with the monoclonal antibody A2B5, which had been shown to recognize the *c*-series ganglioside, GQ1c (Emory et al. 1987). Subsequently A2B5 was shown to react with gangliosides other than those in the *c*-series, and with sulfatides (Majocha et al. 1989) and even with glycoproteins having α 2,8-trisialic acid units (Inoko et al. 2010). In this context, our specific anti-*c*-series ganglioside antibodies definitely demonstrated the presence of the fetal gangliosides in Alzheimer’s brains. This finding was strengthened by the evidence that another fetal antigen, microtubule-associated protein 5 (MAP5), colocalized with *c*-series gangliosides in NFTs (Takahashi et al. 1991). The expression of fetal antigens such as *c*-series gangliosides and MAP5 may indicate that neuronal regeneration (cell proliferation and sprouting) occurs along with neuronal degeneration in the Alzheimer’s brain. Evidence for the regeneration in the Alzheimer’s brain was also provided by the observation of increased dendritic

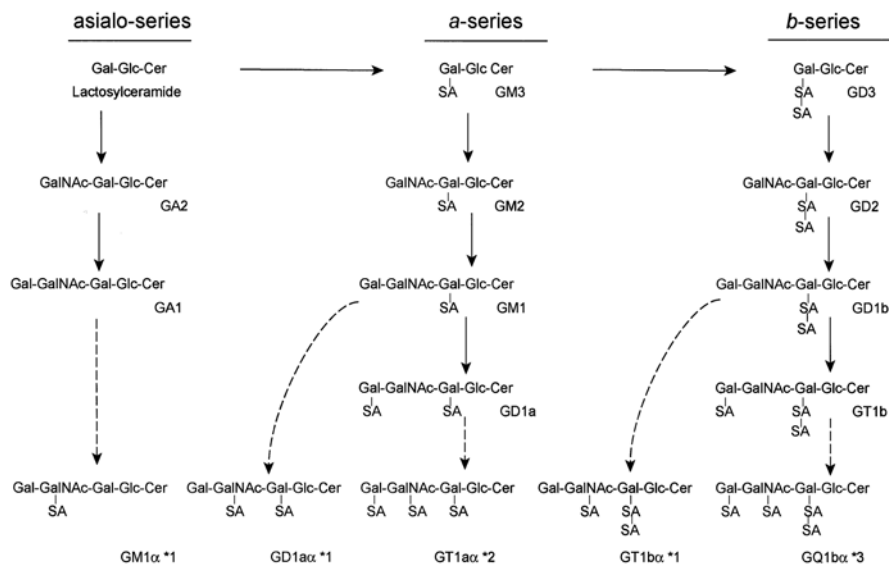


Fig. 19.2 Synthetic pathways for α -series gangliosides (Chol-1 α antigens). Dashed lines indicate sialylation reactions catalyzed by sialyltransferase VII that catalyzes formation of sialyl 2-6 *N*-acetylgalactosamine linkages. Alpha-series of gangliosides marked by *1, *2, and *3 were characterized as Chol-1 α by Irie et al. (1996), Ando et al. (1992) and Hirabayashi et al. (1992), respectively

sprouting and arborization (Probst et al. 1983; Scheibel and Tomiyasu 1978). These findings are consistent with the concept that neuronal regeneration does occur while degeneration proceeds (Lopez-Toledano and Shelanski 2004; Uchida 2010). As the brain has innate plasticity, it is possible that development of synapses achieved by various interventions may help protect the brain from degenerative insults and to recover from their damage (Ando 2012).

19.3.3 Functional Significance of α -Series Gangliosides in Alzheimer's Disease

Whittaker and his colleagues (Richardson et al. 1982) found that cholinergic-specific antigens in the Chol-1 family, comprised of Chol-1 α , Chol-1 β , and Chol-1 γ , were gangliosides. We isolated and characterized two molecular species corresponding to Chol-1 α , termed GT1 α and GQ1 α as illustrated in Fig. 19.2 (Ando et al. 1992; Hirabayashi et al. 1992). The " α " in the abbreviations is assigned to the unique branching structure of a sialic acid residue linked α 2-6 to the *N*-acetylgalactosamine in the gangliotetraose backbone (Taki et al. 1986). Immunostaining indicated that Chol-1 α was present in cholinergic nuclei such as the septal nucleus (Irie et al. 1994). To examine the involvement of gangliosides in

the function of cholinergic synapses, a series of monoclonal antibodies against gangliosides were tested for their ability to suppress release of acetylcholine. Only the anti-Chol-1 α antibody, GGR-41, affected acetylcholine release (Ando et al. 2004). To ascertain its mechanism of action, choline uptake and acetylcholine synthesis were measured using synaptosomes in the presence of GGR-41. Both choline uptake and acetylcholine synthesis were inhibited in a dose-dependent manner by GGR-41. When Chol-1 α was added to a synaptosomal fraction, it accelerated high affinity choline uptake into synaptosomes and this resulted in enhancement of acetylcholine synthesis. These observations led to the question of whether Chol-1 α gangliosides participated physiologically in the cognitive function of the brain. To answer this, GGR-41 was continuously infused into the rat brain septal area in order to disrupt the septohippocampal cholinergic pathway (Ando et al. 2004). This resulted in a reduction in the learning ability of the rats similar to that seen in rats given mecamylamine, a nicotinic cholinergic receptor antagonist. Memory retention was also severely impaired in rats infused with GGR-41. Chol-1 α is thought to localize with nicotinic acetylcholine receptors because it was originally found in torpedo electric organs composed of pure nicotinic nerve terminals (Richardson et al. 1982). In sum, Chol-1 α functions to accelerate acetylcholine turnover in cholinergic synapses and serve as a cholinergic marker.

Expression of Chol-1 α antigens is known to be developmentally regulated as they appear at the time of cholinergic synapse formation in the rat brain (Derrington and Borroni 1990). Neurogenesis and neuronal regeneration are enhanced in cholinergic lesioned brains (Ho et al. 2009) and by environmental stimulation in aged brains (Nakamura et al. 1999). Expression of fetal *c*-series gangliosides in Alzheimer's brains may also reflect neuronal plastic responses (Section 19.3.2). To examine possible alterations in ganglioside metabolism in relation to Alzheimer's disease, animal models with disrupted ganglioside biosynthesis have been developed (Ariga et al. 2010, 2011, 2013; Bernardo et al. 2009; Oikawa et al. 2009). Ganglioside changes were analyzed in brains from double transgenic (Tg) mice that coexpressed amyloid precursor protein with the Swedish mutation and presenilin-1 with a deletion of exon 9 (Ariga et al. 2010). No significant changes were detected in the concentration and composition of major gangliosides in brains from the double-Tg mice. In contrast, expression of cholinergic gangliosides such as GT1 α and GQ1 β (Chol-1 α antigens) increased. Their increased expression may reflect cholinergic neuronal regeneration response to damages induced by A β . The above double-Tg mice were cross-bred with GD3S(St8sia1)^{-/-} mice to generate mice deficient in GD3-synthase responsible for synthesis of *b*-series gangliosides (Fig. 19.1) (Bernardo et al. 2009). In the triple-Tg brains all the *b*-series gangliosides including GD3 were absent, while GM1 and GD1a were increased. Surprisingly, triple-Tg mice showed memory performance similar to that of wild-type control and GD3S^{-/-} mice, while the double-Tg mice exhibited cognitive impairments. Consistent with normalized cognition, A β plaques were almost eliminated. These results indicate that *b*-series gangliosides may be one of the causes of A β accumulation. Remarkably in the triple-Tg brain, the concentration of GT1 α was elevated, while no expression of GQ1 β was observed. Thus, the elevated cholinergic ganglioside GT1 α may

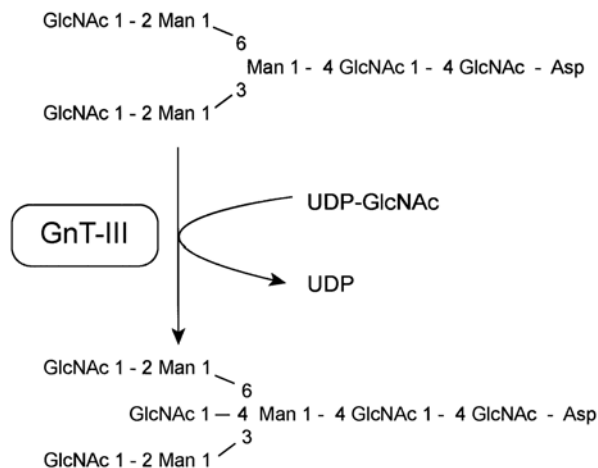


Fig. 19.3 Bisecting GlcNAc residues in N-glycans synthesized by *N*-acetylglucosaminyltransferase III (GnT-III)

contribute to memory retention (Ariga et al. 2013). The double-Tg mice expressing human amyloid precursor protein having the Swedish and London mutations were crossbred with GM2-synthase knockout mice (Oikawa et al. 2009). The mutant mice expressing a large amount of GM3 but not GM1 showed a remarkable increase of A β deposition in vascular tissues (amyloid angiopathy). This observation may indicate another mechanism exists for A β deposition than that covered by the hypothesis that GM1-bound A β is involved in amyloid fibril formation (Kakio et al. 2001) (Sect. 19.3.1). These results indicate that the significance of gangliosides relevant to the physiology and pathology of the brain cannot be deduced simply from studies of the loss-of-function or gain-of-function of each ganglioside. Further comprehensive studies are needed.

19.3.4 Glycoproteins: In Connection with Alzheimer's Disease

Core N-glycosylation and N-glycans were reported to modulate the synthesis of amyloid precursor protein (Pahlsson et al. 1992), suggesting that N-glycosylation status might affect the metabolic pathway of amyloid precursor protein (APP). Analysis of the N-glycan structures determined of mutant amyloid precursor proteins (Swedish type and London type) produced by transfected C17 cells showed that they contained higher contents of bisecting *N*-acetylglucosamine (GlcNAc) residues than normal APP (Akasaka-Manyo et al. 2008). To examine the reason for overexpression of the bisecting structure, expression of *N*-acetylglucosaminyltransferase III (GnT-III)-mRNA (GnT-III is the enzyme responsible for synthesizing bisecting GlcNAc residues) (Fig. 19.3) was measured and found to be increased in Alzheimer's brains (Akasaka-Manyo et al. 2010).

Incubation of Neuro2a cells with A β 42 increased GnT-III gene expression. In a separate setting, Neuro2a cells transfected with a GnT-III expression vector downregulated A β production. Fiala et al. (2007) reported that blood monocytes exposed to A β peptides upregulated transcription of GnT-III and increased A β clearance by phagocytosis. Thus, upregulation of GnT-III appears to exert two effects: inhibition of A β production in neurons and enhancement of its clearance by monocytes. Both responses can be protective against the further progression of Alzheimer's disease.

The possible mechanisms by which bisecting GlcNAc residues could reduce A β production include the following (Akasaka-Manyá et al. 2010): (1) Addition of bisecting GlcNAc may affect the conformation of the APP, thereby inducing changes in its susceptibility to α -, β -, and/or γ -secretases. (2) The increase of bisecting GlcNAc on the APP leads to changes in its N-glycan structure such as diminished degrees of elongation, branching, and sialylation. (3) Bisecting GlcNAc affects trafficking of the APP and, as a result, its susceptibility to secretases. This is supported by the report that localization and trafficking of APP is affected by its glycan modifications (McFarlane et al. 1999). (4) The bisecting GlcNAc directly affects secretase activities. Support for this possibility was provided the observations that (a) enzyme activities of α - and β -secretases were significantly increased and decreased, respectively, in GnT-III-transfected Neuro2a cells (Akasaka-Manyá et al. 2010); (b) Western blot analysis indicated that changes in N-glycan structures were present in the secretases (TACE and BACE). These findings may account for changes in secretase activities and resultant inhibition of A β formation.

19.3.5 Glucocerebrosidase Gene Mutations as a Risk Factor for Parkinson's Disease

Some patients with Gaucher disease were found to develop parkinsonism (Mitsui et al. 2009; Rhouma et al. 2012; Sunwoo et al. 2011). Gaucher disease is an autosomal recessive, lysosomal storage disease caused by mutations in the β -glucocerebrosidase gene (Beutler and Grabowski 1995). Glucocerebrosidase (GBA) is a lysosomal enzyme that catalyzes the hydrolysis of glucocerebroside to ceramide and glucose. Homozygous mutations in the GBA that affect its activity result in accumulation of glucocerebroside in various tissues. Heterozygous loss of function mutations at the GBA locus are a potent risk factor for Parkinson's disease (PD) (Lwin et al. 2004) as evidenced by the finding of multiple cases of parkinsonism among Gaucher disease carriers (Goker-Alpan et al. 2004).

An international collaborative study was done to ascertain the frequency of GBA mutations in ethnically diverse patients with PD (Sidransky et al. 2009). Sixteen centers participated, including five from the Americas, six from Europe, two from Israel, and three from Asia. Two GBA mutations, L444P and N370S, were found in 15.3 % of Ashkenazi Jewish patients with PD, and in 3.2 % of non-Ashkenazi patients indicating a strong association between GBA mutations and PD. When a complete sequence analysis of the variants was carried out for a large cohort of

European, mostly French, patients with PD (Lesage et al. 2011), the results revealed that carrier frequency in the non-Ashkenazi Jewish populations was 7 %, much higher than that, the 3.2 %, reported by the above 16 centers' study (Sidransky et al. 2009). These results indicate that limited screening might miss more than half of the mutant alleles. They also showed that GBA mutations were significantly more frequent (odds ratio=6.98, 95 % confidence interval 2.54–19.21; $p=0.00002$) in PD than in controls. After the 16 centers' study, resequencing of GBA was performed for Japanese patients with PD. The frequency of pathogenic variants in the heterozygous state was shown to be 9.4 % in Parkinson's patients compared to 0.37 % in controls (odds ratio, 28.0). Mutations in the GBA gene are hypothesized to accelerate the pathogenesis of PD (Clark et al. 2007). Support for this was provided by the observation that GBA carriers had a 2.5 year earlier age of onset of PD compared to noncarriers. Although genetic research in the past delineated many mutations that cause PD, such as those in genes encoding E3 ubiquitin ligase parkin (PARK2), leucine-rich repeat kinase 2 (LRRK2), and alpha-synuclein (Bras et al. 2008), research on GBA mutations supports the idea that they are the most common genetic risk factor for PD (Lesage et al. 2011; Neumann et al. 2009).

To address the question of what deleterious effects are caused by GBA mutations, cerebral metabolic activity was assessed in carriers of the GBA mutation both with and without parkinsonism using positron emission tomography (Kono et al. 2010). All GBA mutation carriers had significantly decreased glucose metabolic rates in the supplemental motor area (cortex region anterior to the primary motor cortex), and the carriers with parkinsonism showed additional hypometabolism. The hypometabolism in the cortex region may be related to the clinical manifestation of parkinsonism. Measurement of GBA activity showed it decreased significantly in brains of Parkinson's patients carrying heterozygous GBA mutation (Gegg et al. 2012). The greatest deficiency was found in the substantia nigra (58 % decrease) known to be affected in PD. In PD the brain loses dopaminergic neurons which results in severe reduction in the dopamine content of the striatum (Hornykiewicz 1966). Protein levels of GBA were also reduced, indicating that the lowered expression of the enzyme as well as its decreased activity could contribute to its deficiency (Gegg et al. 2012). Immunofluorescence studies on brain tissues from patients with PD associated with GBA mutations showed that the enzyme was present in 75 % of Lewy bodies while GBA-positive Lewy bodies were found in only 4 % of the subjects without mutations (Goker-Alpan et al. 2010).

Possible mechanisms for the link between GBA gene mutations and PD have been speculated. Mutations in α -synuclein are known to result in aberrant aggregation of the protein, which is associated with neuronal death. The aggregated polymers are proposed to be necessary prerequisites for Lewy body formation seen in PD (Ishizawa et al. 2003). Functional loss of GBA in primary cultured neurons was found to compromise lysosomal protein degradation, cause accumulation of α -synuclein, and result in neurotoxicity through aggregation-dependent mechanisms (Mazulli et al. 2011). These results indicate that increased glucosylceramide, the GBA substrate, directly influences amyloid formation of α -synuclein. Increased glucosylceramide due to a deficiency of GBA is speculated to disrupt the membrane

binding of α -synuclein, enhancing its aggregation in the cytoplasm (DePaolo et al. 2009). Another theory about the relationship of GBA to PD involves its interference with the clearance of mutated proteins. Since most mutations in GBA are missense mutations, the protein likely becomes aberrantly folded and as a result undergoes parkin-mediated poly-ubiquitination and subsequent proteasome-mediated degradation. The presence of mutant GBA might cause build-up of other parkin substrates, causing endoplasmic reticulum-stress and eventual apoptosis of the neurons (Westbroek et al. 2011). Finally, a physical linkage between α -synuclein and GBA was verified using immunoprecipitation and immunofluorescence (Yap et al. 2011).

19.3.6 Gangliosides: In Relation to the Pathogenesis of Parkinson's Disease

The symptoms of PD are manifested after dopaminergic innervation of the striatum is lost as a result of degeneration of dopaminergic neurons in the substantia nigra (Hornykiewicz 1966). Over two decades ago GM1 was hypothesized to act as a neurotrophic factor for dopaminergic neurons (Schneider et al. 1992). A comprehensive review on degenerative diseases and the therapeutic potentials of gangliosides are described in Chap. 20. A causative aspect of reduced gangliosides in PD is partly discussed here. Recently Using a genetic mouse model of Parkinson's disease in which major gangliosides were depleted Ledeen's group (Wu et al. 2011) proved that GM1 was involved in the pathogenesis of parkinsonism. The knockout mice were generated by disrupting the B4galnt1 gene for GM2/GD2 synthase thereby eliminating synthesis of GM2, GD2, and all gangliotetraose gangliosides. The B4galnt1^{-/-} mice manifested clinical parkinsonism and the pathological loss of dopaminergic neurons in the substantia nigra. The symptoms of parkinsonism were largely attenuated by administration of a GM1 analogue, LIGA-20, developed by Costa's group (Manev et al. 1990). This finding supports the hypothesis that GM1 is involved in the pathogenesis of PD. Ledeen's group (Wu et al. 2012) also found that heterozygous mice with one defective allele for the B4galnt1 gene displayed virtually the same degree of parkinsonism as the knockout mice. Interestingly, the levels of GM1 and GD1a, *a*-series gangliosides (Fig. 19.1), decreased in the heterozygous mice by 43 % and 46 %, respectively, while those of *b*-series gangliosides did not significantly decrease. Loss of dopaminergic neurons was evident in the heterozygous mice, and dopamine levels in the striatum decreased progressively as the animals aged. Treatment with LIGA-20 increased the number of tyrosine hydroxylase-positive neurons in the substantia nigra and levels of dopamine in the striatum, indicating recovery of dopaminergic neurons. Combined these observations indicate that the heterozygous mouse model carrying the mutant B4galnt1 gene will be quite useful in future studies of PD.

In human PD, the number of dopaminergic neurons in the substantia nigra, identified by staining for tyrosine hydroxylase, decreased by 40 % compared to that in controls (Wu et al. 2012). Quantification of dopaminergic neurons expressing

GM1 in 11 Parkinson's patients revealed a noticeable GM1 deficiency: 19.7 % of dopaminergic neurons in the patients compared to 61.8 % in controls. This provides an interesting parallel to the deficit of GM1 observed in the heterozygous mouse model discussed above. GM1 staining with cholera toxin B-FITC (specific for GM1) was significantly decreased in both nondopaminergic neurons as well as dopaminergic neurons in Parkinson's brain sections, indicating the widespread abnormal expression of gangliosides in the diseased brain. Not addressed is whether the decreased GM1 is the cause for or result of PD. So far no mutations of genes involved in ganglioside metabolism have been identified as risk factors for PD.

Anti-GM1 ganglioside antibodies have been found in the sera of patients with neurological diseases such as lower motor neuron syndromes (Pestronk et al. 1990; Sunwoo et al. 2011), amyotrophic lateral sclerosis (Pestronk et al. 1988; Rhouma et al. 2012), and Alzheimer's (Chapman et al. 1988; Saito et al. 2002). In an early survey of a limited number of parkinsonian demented patients high titers of anti-GM1 antibodies were found (Saito et al. 2002). Subsequently Zappia et al. (Zappia et al. 2002) studied a large group of PD patients, most of whom had a tremor-dominant form of the disease, and found that more than one-quarter had sera with increased levels of IgM anti-GM1 antibodies. It is hypothesized that increased anti-GM1 antibodies could affect the function of ganglioside GM1 in dopaminergic neurons. Anti-ganglioside immune responses are speculated to contribute to axonal damage via a T cell-mediated mechanism in multiple sclerosis (Pender et al. 2003; McFarlane et al. 1999). When patients with lower motor neuron syndromes and high serum titers of IgM anti-GM1 antibodies were subjected to repeated plasma exchanges (Pestronk et al. 1994; Beutler and Grabowski 1995), removal of the antibodies brought about progressive improvement in muscle strength. These findings indicate that anti-ganglioside antibodies may act as a risk factor for neuronal dysfunction or disease pathogenesis.

19.4 Strategies for Anti-Aging and Prevention of Age-Related Diseases

Studies of glycoconjugates expression and aging have provided much information (Sects. 19.2 and 19.3), and some may provide the basis for development of future therapeutics. Possibilities include use of the knowledge for inducing remyelination, clearance of A β from the brain, and enhancement of innate neuronal plasticity.

19.4.1 Myelin Repair and Remyelination

The fact that the volume of white matter decreases in senescence (Walhovd et al. 2005) indicates that enhanced demyelination occurs in aging brains and more severely in demyelinating disease brains (Zhang et al. 2011). Cognitive declines

appear to correlate with altered myelination of nerve tracts (Aine et al. 2011; Schulze et al. 2011). While disruption of mature myelin is going on, remyelination takes place (Peters and Sethares 2003). This is supported by observations indicating that the number of myelin lamellae increase (Peters et al. 2001) and intermodal lengths of myelin get shorter with advancing age (Bowley et al. 2010). To enhance myelin repair or remyelination following demyelination, promoters of remyelination have been examined as potential therapeutics. The age-associated inefficiency of remyelination (Shields et al. 1999) is known to be due to impairment of both recruitment and differentiation of oligodendrocyte progenitor cells (OPC) (Sim et al. 2002). Myelin synthesis is preceded by downregulation of OPC differentiation inhibitors such as PSA-NCAM (Shen et al. 2008). This downregulation is epigenetically controlled by recruitment of histone deacetylases to promoter regions, indicating that efficient remyelination requires deacetylation of nucleosomal histones. Epigenetic control of remyelination is potentially an important therapeutic target. Another promising intervention to enhance remyelination is hormonal stimulation of OPC (Calzà et al. 2010; Fernandez et al. 2004). Thyroid hormone was shown to regulate proliferation and differentiation of OPC and induce myelinating oligodendrocytes. Actually, systematic administration of thyroid hormone enhanced myelination in an experimental allergic encephalomyelitis model (Fernandez et al. 2004) as well as in a cuprizone-induced demyelination model (Franco et al. 2008). Using an *in vivo* deuterium labeling method (Ando et al. 2003) thyroxine was found to enhance incorporation of ganglioside GM1 into mature myelin of adult mice (Ando et al. 1984).

19.4.2 Acceleration of A β Clearance

Aging is the major risk factor for neurodegenerative diseases such as Alzheimer's disease and PD (Sect. 19.3) with accumulation of aberrant precipitates of amyloid- β peptide in brains from the former and α -synuclein in those from the latter. Clearance of those toxic compounds from the brain is driven by an active transport system at the blood–brain barrier (BBB) and blood–cerebrospinal fluid barrier. In the transport system at the barriers, the receptor low-density lipoprotein receptor-related protein 1 takes up the toxic compounds at the abluminal sites of capillary endothelial cells, and P-glycoprotein (P-gp) at the luminal sites of the cells excretes them into the blood stream. Decreased function of P-gp was observed in Alzheimer's patients (Vogelgesang et al. 2004) and in Parkinson's patients (Bartels et al. 2008). The expression of P-gp decreases in the BBB with age (Silverberg et al. 2010). As the reduced clearance of amyloid- β across the BBB is thought to enhance amyloid accumulation, a decrease in P-gp could be a risk factor for developing Alzheimer's disease. In this context, development of a model to upregulate expression of P-gp and enhance clearance of amyloid- β could provide a new method for treating Alzheimer's disease. Support for this idea was provided by both *in vitro* (Abuznait et al. 2011) and *in vivo* studies (Hartz et al. 2010).

Serum amyloid P (SAP) is also thought to be involved in the pathogenesis of Alzheimer's disease. SAP, a member of the pentraxin family, is a glycoprotein secreted by the liver into the blood stream. The main functions of SAP are to recognize carbohydrates, nuclear substances, and amyloid fibrils (Agrawal et al. 2009). SAP does not cross the BBB, however, neurons produce it in the brain, and its production is upregulated in Alzheimer's brains (Yasojima et al. 2000). SAP is assumed to contribute to the pathogenesis of Alzheimer's disease by binding to amyloid plaques and entering neurons to induce apoptotic cell death (Ulbanyi et al. 2003). Although the hallmarks of Alzheimer's disease include amyloid plaques and neurofibrillary tangles, a significant population of individuals who have plaques and tangles have no signs of cognitive impairment. Crawford et al. (2012) measured SAP levels in the hippocampus and cerebral cortex of post mortem samples obtained from Alzheimer's patients and nondemented individuals with Alzheimer's neuropathology, and found that the latter had no significant difference in SAP levels compared to normal controls while the former had increased SAP levels. The lack of dementia in individuals with Alzheimer's neuropathology and low levels of SAP, a marker of inflammation, may be due to reduced inflammatory responses. From the therapeutic point of view, reduction of the increased serum SAP might be beneficial for Alzheimer's patients. Pepys et al. (2002) invented a drug, R-1-[6- [R-2-carboxypyrrolidin-1-yl]-6-oxo-hexanoyl] pyrrolidine-2-carboxylic acid that is a competitive inhibitor of SAP binding to amyloid fibrils. Kolstoe et al. (2009) administered it to patients with probable Alzheimer's disease for 12 weeks, and found that the SAP concentrations in serum and cerebrospinal fluid were significantly reduced. Their trial was too short to provide measurable neurological or cognitive effects.

19.4.3 Gene-Transfer of Enzymes Responsible for Glycoconjugates

Loss of function mutations at the GBA locus is a known risk factor for PD (Lwin et al. 2004) (see Sect. 19.3.5). Sardi et al. (2011) developed mouse models of Gaucher disease including homozygote ($Gba1^{D409V/D409V}$) and heterozygotes ($Gba1^{D409V/+}$ and $Gba1^{+/-}$) that showed loss of GBA activity. GBA activity was reduced in homozygous mice (19 % of that of wild type) and heterozygous (59 % for $Gba1^{D409V/+}$ and 54 % for $Gba1^{+/-}$). Adeno-associated virus-mediated expression of exogenous GBA in the hippocampus of homozygous mice brought about remarkable amelioration of both the neuropathology and memory deficits. Sardi et al. (2013) developed a transgenic mouse model overexpressing A53T α -synuclein and using it found that augmented striatal expression of exogenous GBA in the mice reduced the levels of both cytosolic soluble α -synuclein and membrane-associated striatal α -synuclein.

The observation that PSA-NCAM (see Sect. 19.2.5) was expressed concurrently with sprouting of injured or axotomized Purkinje cells in glial scars (Dusart et al. 1999) led to interrogation of whether induction of PSA expression in damaged

tissues in adult CNS could enhance neuronal regeneration. To test the therapeutic potential of PSA, a viral vector encoding polysialyltransferase was employed to transfect scar astrocytes and sustain expression of high levels of PSA (El Maarouf et al. 2006). This resulted in substantial growth of axonal processes through the spinal injury site. Induced expression of PSA may be a promising strategy for promoting neural tissue repair. Similar genetic manipulations using viral vectors encoding GnT-III (see Sect. 19.3.4) could be applied to Alzheimer's brains to inhibit amyloid β production and to enhance the clearance of amyloid β as previously suggested (Akasaka-Manya et al. 2010). A possible alternative would be to use the curcumin derivative, bisdemethoxycurcumin found to induce expression of GnT-III (Fiala et al. 2007).

19.4.4 Ganglioside Analogues and Environmental Effectors of Neuronal Plasticity

Gangliosides, sialic acid-containing GSLs, are important mediators of neuronal function, age-related neuronal dysfunction, and Alzheimer's pathology. Studies have shown that gangliosides may mimic nerve growth factor neurotrophic activity thereby restoring cholinergic parameters (Cuello et al. 1989; Ferrari et al. 1995; Mutoh et al. 1995; Rabin and Mocchetti 1995). The beneficial effects of ganglioside GM1 were shown in the experimental models of glutamate neurotoxicity (Favaron et al. 1988; Vaccarino et al. 1987; Wu et al. 2005), brain and spinal cord lesions (Geisler et al. 1991; Oderfeld-Nowak et al. 1993), and cerebral ischemia (Seren et al. 1990). Although gangliosides have been hypothesized to serve as neuroprotective agents capable of reducing brain and spinal cord damages in disease conditions, they were proven to attenuate neuronal apoptosis induced by serum deprivation, ionomycin, or cyclosporine A in an in vitro system (Ryu et al. 1999). However, gangliosides did not attenuate neuronal necrosis induced by exposure of cultured cortical cells to excitotoxins, and even increased necrosis induced by oxidative stress. Thus, gangliosides seem to rescue neurons from becoming apoptotic.

Two decades ago, GM1 was reported to activate the TrkA (tropomyosin-related kinase A) receptor (Ferrari et al. 1995; Mutoh et al. 1995; Rabin and Mocchetti 1995). Later it was shown to activate TrkC by inducing release of neurotrophin-3 (Rabin et al. 2002). In contrast to GM1 which induces neurotrophin-3 but not BDNF, a synthetic analogue of GM1, LIGA20 (Manev et al. 1990), was found to increase secretion of BDNF by stimulating TrkB in NIH-3T3 fibroblasts. When the same amount of GM1 and LIGA20 were given orally to rats, the concentration of LIGA20 in the brain was 50-fold higher than that of GM1 (Polo et al. 1994). This may account for the superior potency of LIGA20 compared to natural GM1.

LIGA20 is similar in structure of lyso-GM1 (Manev et al. 1990). Although LIGA20 appears to be membrane permeable, it was hypothesized that smaller molecules would be more suitable for transportation across the BBB. To address this sialylcholesterol was synthesized (Sato et al. 1987). Effects of the two stereoisomers,

α - and β -sialylcholesterols, on cholinergic synapses were examined (Tanaka and Ando 1996) to determine whether they could ameliorate age-related decrements in synaptic functions observed in studies of mouse brain synaptosomes (Tanaka et al. 1996). While both isomers enhanced acetylcholine release from synaptosomes, their underlying mechanisms differed. Alpha-sialylcholesterol increased depolarization-induced influx of calcium ions to enhance acetylcholine release, while not affecting choline uptake. On the other hand, β -sialylcholesterol activated high-affinity choline uptake, resulting in enhancement of acetylcholine synthesis followed by augmentation of acetylcholine release. The β -isomer had no effect on calcium ion influx. These results imply that the two isomers of sialylcholesterol modulate the synaptic functions in different ways, and that their effects on cholinergic synaptic transmission are synergistic. The results also indicate that the actions of the synthetic sialylcholesterols on synapses mimic those of naturally occurring gangliosides (Ando et al. 1998). The action of the α -isomer on calcium channels appears to be similar to that observed using ganglioside GQ1b. In contrast, the β -isomer activation of the choline transporter was similar to the effect of the Chol-1 α ganglioside (see Sect. 19.3.3). The similarity of the effects of both gangliosides and sialylcholesterols on synaptic action is summarized in a review (Ando 2012).

Neuronal plasticity, a crucial requirement for adapting to new environments, developing neuronal integrity, and restoring damaged neural architecture, are central themes in basic and clinical neuroscience. Age-related deterioration in brain functions or damage caused by neurodegenerative diseases or various insults can be partly restored by innate neuronal plasticity. Stimulation of plasticity can be considered the ultimate strategy for maintaining brain function during aging and for its efficient recovery from neuronal damage. Synaptic plasticity was enhanced as revealed by increased synaptogenesis and cognitive improvement when aged rats were put in an enriched environment (Ando 2012; Saito et al. 1994). In a mouse model of PD, physical activity and environmental enrichment stimulated oligodendrocyte differentiation in the substantia nigra, again indicating their positive effect on cellular plasticity (Klaissle et al. 2012). Neuronal plasticity is thought to be regulated by at least two groups of molecules: neurotrophins and adhesion molecules. The effect of activity on plasticity may be explained by the observation that expression of BDNF and NCAM were upregulated in the spinal cords of rats given exercise (Macias et al. 2002). Drugs can also affect neuronal plasticity. Warfarin is routinely prescribed for patients with atrial fibrillation or cerebral infarction, but since it is also a vitamin K antagonist and may cause vitamin K-deficiency it must be used with care. The first indication that vitamin K was needed by the nervous system was the observation by Sundaram and Lev (1988) that young mice fed warfarin had decreased brain concentrations of sulfatide due to reduced activity of galactocerebroside sulfotransferase, needed for its synthesis (Fig. 19.1). Lifelong intake of a low-vitamin K diet was shown to impair cognitive performance by old rats. They also had low levels of gangliosides in the pons medulla and midbrain (Carrié et al. 2011). Sulfatide contents were not different between high- and low-dosed groups in old rats. In humans, fetal exposure to warfarin is known to induce warfarin embryopathy identified by symptoms such as blindness and mental

retardation due to optic and cerebral atrophies (Hall et al. 1980). Patients with early stage Alzheimer's disease were found to have significantly lower intakes of vitamin K compared to age- and gender-matched controls (Presse et al. 2008). With regard to brain plasticity or responsiveness, both positive and negative environmental risk factors such as enriched environment and warfarin must be considered.

19.5 Concluding Remarks

In Sect. 19.2, age-related changes in glycoconjugates, mostly GSLs and glycoproteins, in the central nervous system are summarized.

In Section 3, new findings on the pathogenesis of age-related neurodegenerative diseases such as Alzheimer's and Parkinson's are discussed. Ganglioside GM1 may function as a seed for amyloid fibril formation, and the expression of Chol-1 α gangliosides in the Alzheimer's model mouse brain is thought to be a compensatory response to restore cholinergic function. Evidence suggests that mutations in the gene for GBA and partial deficits in α -series gangliosides may contribute to PD.

In section 4, possible strategies for anti-aging and the prevention of age-related dementia are discussed, including those to (1) enhance remyelination, (2) enhance clearance of amyloid- β , and (3) express the GBA gene. To ameliorate the functional deficits in aging and diseased brains, ganglioside-analogues, LIGA20 and sialyl-cholesterols, have been tested. Alpha- and β -stereoisomers of the latter are found to activate calcium ion channels and high-affinity choline uptake at presynapses, respectively. Finally, environmental factors (eg physical activity and drugs) affecting neuronal plasticity in relation to glycoconjugates are discussed.

Conflict of Interest The author declares no conflicts of interest in preparing this article.

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