Chapter 20
Gangliosides and Glycolipids in Neurodegenerative Disorders

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Abstract Glycolipids and gangliosides play important roles in maintaining the functional integrity of the nervous system. However, surprisingly little is known about how glycolipids and gangliosides in particular participate in various neurodegenerative processes. For example, it has been known for a long time that administration of gangliosides and in particular, GM1 ganglioside, can ameliorate damage to the central and peripheral nervous systems and can mitigate effects of a variety of neurodegenerative processes. What is not known is the extent to which dysfunctional biosynthesis or metabolism of gangliosides may be involved in various neurodegenerative disorders and if alterations observed reflect an intrinsic disease-related process or represent the response of the brain to a degenerative process. This chapter briefly reviews recent advances in the study of glycolipids and gangliosides and their potential participation in a variety of neurodegenerative disorders including Parkinson's disease, Alzheimer's disease, Huntington's disease and the potential link between Gaucher disease and Parkinson's disease.

Keywords Gangliosides • Glycolipids • Parkinson's disease • Huntington's disease • Alzheimer's disease • Gaucher disease

Abbreviations

AD	Alzheimer's disease
CNS	Central nervous system
Ca	Calcium

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mg/kg	Milligram per kilogram
TH	Tyrosine hydroxylase
HVA	Homovanillic acid
MPTP	1-Methyl-4-phenyl 1,2,3,6-tetrahydropyridine
UPDRS	Unified Parkinson's Disease Rating Scale
APP	Amyloid precursor protein
Aβ	Amyloid-beta
BACE1	Beta-secretase 1
DARP-32	Dopamine- and cAMP-regulated neuronal phosphoprotein
GBA1	Beta-glucosidase 1

Glycolipids are broadly defined as lipids with a carbohydrate attached. There are a wide variety of glycolipids found in biological systems. Of particular relevance for the nervous system is a subset of glycolipids known as glycosphingolipids that contain sphingosine. A further subset of glycosphingolipids of particular relevance to the structure and function of the nervous system are cerebrosides and gangliosides. Glycosphingolipids are present on cell surface membranes and are particularly abundant in the brain (Hirabayashi 2012). Cerebrosides comprise a group of glycosphingolipids consisting of ceramide and sugar residues, the major forms being glucocerebrosides and galactocerebrosides. Gangliosides are sialic acid-containing glycosphingolipids that are integral components of cell surface membranes and are highly enriched in the central nervous system. The major ganglioside species in brain are a- and b-series gangliosides and consist of the major gangliosides GM1, GD1a, GD1b, and GT1b. GM1 ganglioside, a main component of membrane signaling domains (lipid rafts), is particularly important in the central nervous system (CNS) as it plays important roles in neuronal development and survival and modulates a wide variety of cellular functions through modulation of cell signaling mechanisms. GM1 has been shown to exert neurotrophic or neuroprotective effects under a variety of circumstances and influences numerous cellular activities mediated at the level of the plasma membrane as well as intracellularly, where it influences Ca^{2+} homeostasis, mitochondrial function, and lysosomal integrity, among other processes (Hakomori and Igarashi 1993; Allende and Proia 2002; Shield et al. 2006; Wei et al. 2009).

This brief review focuses on recent advances in the description and understanding of the role of glycolipids and in particular, gangliosides and glucocerebrosides, in neurodegenerative disorders. This review focuses on Parkinson's disease, Alzheimer's disease, and Huntington's Disease and the accumulating evidence for a link between Parkinson's disease and Gaucher disease.

20.1 Gangliosides and Parkinson's Disease

GM1 ganglioside has long been suggested as a potential agent for the treatment of Parkinson's disease, although the precise reasons for the efficacy of GM1 in animal models of Parkinson's disease and in Parkinson's disease patients is still unclear.

Toffano et al. (1983) first described the ability of GM1 ganglioside to enhance recovery of the nigrostriatal projection system. In this initial study, administration of GM1 ganglioside (30 mg/kg, beginning the second day after surgery) to rats that received unilateral hemitransections of ascending nigrostriatal dopaminergic fibers significantly increased striatal tyrosine hydroxylase (TH) activity, homovanillic acid (HVA) content, TH immunohistochemical staining ipsilateral to the hemitransection and reduced apomorphine-induced rotations. These data were the first demonstration of improvement of biochemical, morphological, and behavioral parameters associated with damage to the nigrostriatal pathway with GM1 treatment (Toffano et al. 1983). Over the next couple of decades, numerous studies were performed showing that administration of GM1 ganglioside at least partially reversed detrimental effects of various types of insults to the nigrostriatal dopamine system including mechanical transection (Agnati et al. 1983; Toffano et al. 1983, 1984), 1-methyl-4-phenyl, 1,2,3,6-tetrahydropyridine (MPTP) toxin-induced lesions (Hadjiconstantinou et al. 1986; Schneider and Yuwiler 1989; Hadjiconstantinou and Neff 1988), and, 6-hydroxydopamine-induced lesions (Tilson et al. 1988) to the nigrostriatal dopamine system, as well as ameliorate age-related dopaminergic changes in brain. Results in normal aged animals are particularly interesting in that GM1 administration restored a variety of dopaminergic markers in the striatum and substantia nigra to levels approximate to those seen in young animals (Goettl et al. 1999, 2003). Although GM1 administration had little effect on several measures of motor function assessed in aged animals (Goettl et al. 2001), improvements in cognitive functioning (i.e., spatial learning and memory) were described (Fong et al. 1997). Although relatively few papers have examined age-related changes in ganglioside content in brain, in rats, GM1 levels in whole brain were reported to be fairly consistent between 3 and 24 months of age, while GD1a and GT1b levels decreased (Aydin et al. 2000). These data need to be viewed cautiously as there are significant regional differences in ganglioside content in brain that might be obscured by examining whole brain expression. Regional expression of gangliosides examined in human brain showed variation by region and age (between 4 months and 80/90 years of age), with GM1 levels significantly decreased with advanced age in the frontal cortex and moderately decreased in hippocampus (Kracun et al. 1992b), with a possible shift in expression from the a- to b-series gangliosides with aging (see Chap. 19).

While most of the experimental work with GM1 and Parkinson's disease models was performed with rodents, studies using nonhuman primate models of Parkinson's disease also showed significant improvements with GM1 treatment. In MPTP-treated monkeys, GM1 treatment resulted in improved motor and cognitive functioning, compared to saline-treated lesion control animals, and also resulted in small but statistically significant increases in striatal dopamine levels and increased density of tyrosine hydroxylase (TH)-positive fibers (Schneider et al. 1992). Other studies showed that GM1 treatment resulted in significant increases in TH protein levels in residual dopaminergic neurons in the substantia nigra of MPTP-treated monkeys (Herrero et al. 1993).

These promising preclinical research findings led to clinical studies of GM1 treatment in Parkinson's disease patients. All clinical studies using GM1 were

approved by the appropriate institutional ethics committees, performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki, and written informed consent was obtained from all subjects prior to enrollment. Following a small phase I safety study (Schneider et al. 1995b), a randomized, double-blind, placebo-controlled trial was conducted with 45 Parkinson's disease patients ($N=22$ GM1; $N=23$ placebo) over a 16-week study period (Schneider et al. 1998). At the study initiation visit, subjects received intravenous infusion of 1,000 mg GM1 or placebo and then received two subcutaneous injections per day (GM1 100 mg/2 ml per injection or placebo) for the remainder of the 16 week study period. The primary efficacy measure was change from baseline in the Unified Parkinson's Disease Rating Scale (UPDRS) motor score, assessed during a practically defined off period (that is, in the morning after at least 12 h from the last dose of any anti-Parkinson medication). The GM1-treated group showed significant improvements in UPDRS motor scores compared to subjects receiving placebo (Schneider et al. 1998). The treatment effect size at week 16 was -6.79 ± 1.24 ($p<0.0002$). Secondary measures of activities of daily living and performance of timed motor tests also showed significant effects in favor of the GM1-treated subjects (Schneider et al. 1998). GM1 was well tolerated and no serious adverse effects were noted. This brief duration study suggested that GM1 could have a symptomatic effect in Parkinson's disease patients. Although the precise mechanisms underlying this response are not known, the effects observed in this study are consistent with preclinical data demonstrating an ability of GM1 to enhance TH expression and dopamine synthesis in residual neurons in animal models of Parkinson's disease (Herrero et al. 1993; Schneider et al. 1995a).

A group of subjects who completed the study described above consented to continue to receive GM1 and to be followed clinically for up to 5 years (Schneider et al. 2010). In this open extension study (26 subjects at start; 13 from the prior placebo group and 13 from the prior GM1-treated group), subjects were administered a total daily dose of 200 mg GM1 by subcutaneous injection (two injections of 100 mg GM1 per day). Subjects were evaluated during practically defined off periods at 6 month intervals over the course of the study. Changes in UPDRS motor scores and activities of daily living scores were assessed as were timed tests of motor function. In subjects who received GM1 during the previous randomized study, regression modeling showed a slow linear increase of the average UPDRS motor score over time, with an estimated annual rate of increase of approximately 1.2 points (95 % confidence interval, CI: −0.1 to 2.5, $p=0.06$) (Schneider et al. 2010). However, at the end of 5 years of continuous GM1 use, the estimated average UPDRS motor score (for the ten subjects who continued through the entire 5 year period) was still lower than that at baseline prior to randomization into the main randomized trial, suggesting that improvements achieved during the initial study were maintained during the open extension period. In subjects previously randomized to receive placebo but who received GM1 during the open-extension study, regression modeling also showed a change in the average UPDRS motor scores over time. Over the first 2 years of the extension study, motor scores decreased by about 3–4 points per year on average while in later years, the scores increased

slightly and approached pre-randomization levels by the fifth year. However, for nine of the ten subjects followed for the full 5 year period, no appreciable progression of motor symptoms was observed. This relatively small open label study suggested that chronic use of GM1 in PD patients was safe (no serious adverse events reported over the course of the study) and may be beneficial in Parkinson's disease patients. However, without a control group, it is not possible to come to any firm conclusions regarding the long-term efficacy of GM1 as a potential disease modifying agent in Parkinson's disease.

In order to better assess efficacy of GM1 as a potential disease modifying therapy for Parkinson's disease, a randomized, controlled, delayed start trial of GM1 in Parkinson's disease was conducted (Schneider et al. 2013). Due to the complex nature of Parkinson's disease, there are several challenges in the clinical assessment of disease progression and the demonstration of disease modification, since many drugs with potential disease modifying effects may also exert symptomatic effects. Since we had previously shown that GM1 may potentially have both symptomatic and disease modifying effects on Parkinson's disease, a study design, the delayed start study, previously suggested to possibly differentiate between these aspects of drug response (Olanow et al. 2008, 2009; D'Agostino 2009) was used. In the delayed start trial design, subjects are initially randomized to either an early start group (i.e., randomized to receive GM1 and to continue to receive GM1 for the duration of the trial (out to week 120)) or a delayed start group (randomized to receive placebo but switched to GM1 after 24 weeks). In addition, a separate group of standard-of-care subjects ("Comparison group") was recruited according to the same criteria used for recruitment of the treatment groups and these subjects were assessed longitudinally to provide descriptive information regarding disease progression. The primary outcome measure in this study was change from baseline UPDRS motor scores assessed during a practically defined off period. Subjects were also evaluated during their best on period (i.e., typically at least 1 h. after taking their standard anti-Parkinson medication). At week 24, the early-start (GM1) group showed significant improvement in UPDRS motor scores compared to a significant worsening of scores in the delayed-start (placebo) group (Fig. 20.1). The early-start group also showed a sustained benefit compared to the delayed-start group at the end of the study (week 120) (Fig. 20.1). Following an initial improvement in UPDRS motor scores in the early-start group, this measure of symptom severity changed little over the course of the study and by the end of the observation period, these scores were still lower (i.e., improved) than they were at study baseline (Schneider et al. 2013). The standard-of-care comparison group showed a pattern of symptom progression different from both the early-start subjects who received GM1 throughout the study and the delayed-start subjects after they started receiving GM1 after week 24 (Schneider et al. 2013). Both early-start and delayed-start groups showed significant symptom worsening during washout (assessed at 1–2 years after the last use of GM1) (Fig. 20.1). The results of this study supported the previous report that GM1 use for a relatively short period of time was superior to placebo for improving motor symptoms and showed that extended GM1 use (up to 120 weeks) resulted in a lower than expected rate of symptom progression (also

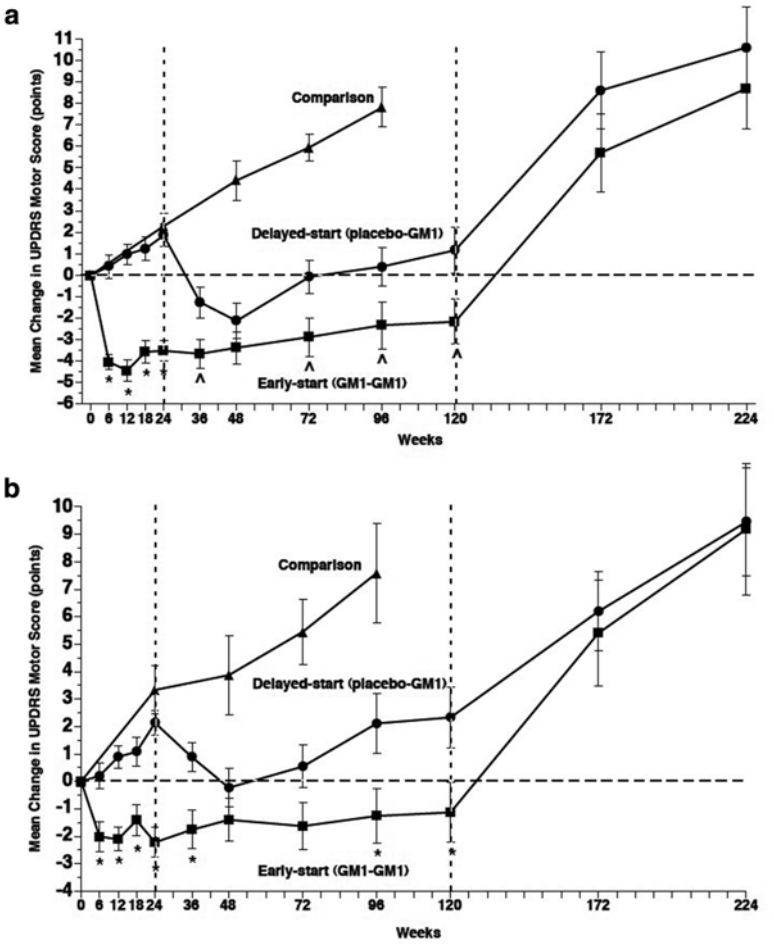

Fig. 20.1 Changes in unified Parkinson's disease rating scale (UPDRS) motor subsection scores. (**a**) The mean (±SE) change from baseline (observed scores) in Early-start and Delayed-start study subjects and in the standard-of-care Comparison group, assessed in the practically defined "off" condition. The *dashed vertical line* at week 24 indicates the end of study Phase I. The *dashed vertical line* at week 120 indicates the end of study Phase II. The *horizontal dashed line* indicates baseline level. An increase of score indicates symptom worsening; a decrease in score indicates symptom improvement. *$p < 0.0001$ Early-start vs. Delayed-start; ^$p < 0.05$ Early-start vs. Delayed-start. (**b**) The mean (±SE) change from baseline in Early-start and Delayed-start study subjects and in the standard-of-care Comparison group, assessed in the best "on" condition. The *dashed vertical line* at week 24 indicates the end of study Phase I. The *dashed vertical line* at week 120 indicates the end of study Phase II. The *horizontal dashed line* indicates baseline level. *$p < 0.01$ Early-start vs. Delayed-start. [Reprinted from Schneider JS, Gollomp SM, Sendek S, Colcher A, Cambi F, and Du W (2013) A randomized, controlled, delayed start trial of GM1 ganglioside in treated Parkinson's disease patients. *Journal of the Neurological Sciences* **324**:140–148

suggested in the previous open label study). Thus, the data from this relatively small study suggested that GM1 may have symptomatic and potentially disease modifying effects on Parkinson's disease.

Despite the positive effects of GM1 on preclinical models of Parkinson's disease and positive effects of GM1 in Parkinson's disease patients, the mechanisms underlying these effects remain somewhat obscure. We have suggested that at least in part, the apparent neuroprotective/neurorestorative effects of GM1 may involve modulation of lipid raft structure/function by altering the GM1 content of the rafts that could exert significant influence on a variety of signaling pathways (Schneider et al. 2013). Further, several Parkinson's disease-relevant proteins such as alpha synuclein, LRRK2, parkin, and PINK1 associate with lipid rafts and co-localize with GM1, potentially influencing neurodegeneration in Parkinson's disease (Martinez et al. 2007; Fallon et al. 2002; Hatano et al. 2007). One reason why GM1 may seemingly work so well in Parkinson's disease is that administration of GM1 to Parkinson's disease patients may represent GM1 replacement therapy, that is, restores a deficiency in GM1 levels (see Chap. 15). This would only be true if there is in fact a decrease in GM1 levels in the Parkinson's disease brain, and specifically, in the nigrostriatal dopamine system. Recent data from our lab (Kidd et al. 2012) and others (Wu et al. 2012) suggest that GM1 levels may be lower than normal in the substantia nigra of Parkinson's disease patients compared to age matched controls. This may be due to lower levels of GM1 in residual neurons. Additionally, we have made the novel observation that expression of key glycosyltransferase genes *B3Galt4* (the gene encoding the glycosyltransferase necessary for conversion of GM2 into GM1) and *St3gal2* (the gene encoding the sialyltransferase necessary for conversion of GM1 into GD1A) are decreased in the substantia nigra in Parkinson's disease brains compared with age-matched controls (Kidd et al. 2012). We have also recently observed increases in gene expression in Parkinson's disease substantia nigra for at least some of the enzymes responsible for the production of both a- and b-series gangliosides (i.e. *St3Gal5*, *St8sia3*, see Chap. 9 for metabolic pathways), compared to samples from neurologically intact, age-matched controls (Mettil et al. 2013). These findings together suggest that in addition to a loss of GM1 in the Parkinson's disease substantia nigra, there may also be an imbalance between a- and b-series gangliosides. More work is needed in order to understand the extent to which there is indeed a defect in GM1 expression in the Parkinson's disease brain and if so, the extent to which this defect is specific to the nigrostriatal dopamine system.

20.2 Gangliosides in Alzheimer's Disease

Several lines of evidence have linked Alzheimer's disease (AD) with aberrant lipid homeostasis and with abnormal expression of gangliosides. There have been a number of reports of decreased ganglioside concentrations in various regions of the AD brain dating back to the late 1960s, but some of these findings have been contradictory and lacked experimental consistency in the way in which gangliosides were

measured and in the pathological confirmation of AD and AD subtypes. Gottfries et al. (1983) described a decreased expression of brain gangliosides in AD brain but the pattern of ganglioside expression was not evaluated. Kalanj et al. (1991) and Kracun et al. (1992a) reported that in AD brain, all ganglio-series gangliosides (i.e., GM1, GD1a, GD1b, and GT1b) were decreased in temporal and frontal cortices as well as in the nucleus basalis of Meynert, while gangliosides GM2, GD3, and GM3 were elevated in frontal and parietal cortex. Svennerholm and Gottfries (1994) described significant decreases in gangliosides in frontal and temporal cortices, caudate nucleus, and hippocampus in AD type I cases (early onset form) and more restricted loss of gangliosides in temporal cortex, hippocampus and frontal white matter in AD type II (late onset) cases. These authors suggested that based on a diminished yield of synaptosomes in AD type I brains that there was marked loss of synapses and neuronal processes in the AD type I brain. Studies examining CSF from AD patients showed increased GM1 in CSF in early onset AD compared to late onset AD, suggested by the authors to indicate more severe neurodegeneration in type I vs. type II AD patients (Blennow et al. 1991).

Recent evidence, however, suggests that more than simple measurement of ganglioside levels in AD brain may be needed to better appreciate the role that gangliosides might play in the pathophysiology of AD. More complex alterations in the lipid profile in brain may be associated with AD, with region-specific lipid anomalies potentially linked to AD pathogenesis (Chan et al. 2012). Aberrant lipid homeostasis has been suggested to play a role in AD as the neuronal lipid composition regulates activity of key proteins such as APP, BACE1 and presenilin that control Aβ levels (Chan et al. 2012). Gangliosides (GM1 in particular) have been suggested to modulate the pathogenic potential of Aβ by influencing its aggregation properties. A number of studies have suggested that the interaction of Aβ with GM1 results in GM1-bound Aβ that acts as a seed for the Aβ fibrillogenesis in the AD brain (Yanagisawa 2007). Recent data further suggest that Aβ is preferentially incorporated into GM1-rich membrane regions (i.e., lipid rafts) where the peptides undergo a conformational shift that disrupts membrane stability and promotes peptide–peptide interaction and oligomer formation (Haughey et al. 2010). Although the precise role of gangliosides and other lipids in AD remains to be determined, it is clear that alterations in sphingolipid metabolism and expression likely play an important role in the pathological processes contributing to AD. The role of GM1 ganglioside in particular in AD remains to be elucidated as some reports suggest that GM1 administration may be at least partially neuroprotective in model systems (Kreutz et al. 2011) and in humans (Svennerholm et al. 2002).

20.3 Gangliosides and Huntington's Disease

Desplats et al. (2007) reported abnormal expression levels of various genes encoding glycosyltransferases and sialyltransferases that are involved in the biosynthesis of various gangliosides in the striatum of Huntington's disease transgenic mice (R6/1 mice) and in postmortem caudate nucleus tissue from Huntington's disease

patients. In particular, increased expression of *St8sia1* (encoding GD3 synthase) and decreased expression of *St8sia2*, *St8sia3* (GD3 synthase) and *B4galnt1* (GM2/GD2 synthase) was found in the striatum of R6/1 transgenic Huntington's disease mice. The mRNA expression levels of *St3gal5* (encoding GM3 synthase), *St3gal2* (encoding GM1b/GD1a/GT1b synthase), and *St6galnac5* (*SiaT7e*) were not affected in the R6/1 transgenic mice (Desplats et al. 2007). Ganglioside analysis showed a significant decrease in GM1 levels in striatum from R6/1 transgenic mice (Desplats et al. 2007). The gene expression of *St3gal5, St8sia3*, *B4galnt1*, and *St3gal2* were significantly decreased in the caudate nucleus from HD patients. However, in human Huntington's disease caudate, an overall decrease in ganglioside levels was reported, compared to control subjects with the exception of a specific increase in GD3 levels (Desplats et al. 2007). This could be significant as GD3 may be an apoptogenic ganglioside (Scorrano et al. 1999) and increased levels of GD3 in Huntington's disease caudate could contribute to apoptotic neurodegeneration. Although these data are from a very small sample of Huntington's patients (i.e., three cases), they do suggest altered ganglioside biosynthesis and expression associated with Huntington's disease.

Following up on these data, Maglione et al. (2010) described decreased expression of *B3galt4* (GM1/GD1b synthase) mRNA and reduced levels of GM1 ganglioside in cell and animal models of Huntington's disease as well as in fibroblasts isolated from Huntington's disease patients (Maglione et al. 2010). They further reported that the presence of mutant huntingtin protein affected ganglioside metabolism in a transgenic mouse Huntington's disease model, with reduced GM1, GD1a, and GT1b levels noted in striatum and cortex (Maglione et al. 2010). Administration of GM1 to a knock-in cell model of Huntington's disease restored GM1 levels and protected cells from apoptosis. GM1 administration also promoted AKT activation and resulted in phosphorylation of mutant huntingtin protein which may support neuroprotection and perhaps decrease toxicity of the mutant protein (Maglione et al. 2010). Importantly, this study demonstrated that relatively small alterations of GM1 content in the plasma membrane could cause significant changes in cell susceptibility to apoptosis.

As a follow up to the findings that levels of GM1 may be decreased in the HD brain (as well as in HD models), Di Pardo et al. (2012) demonstrated that administering GM1 by intraventricular infusion in a mouse HD model ((YAC)128 mice) restored normal motor behavior, increased striatal expression of DARP-32, a protein highly enriched in intrinsic striatal neurons, and increased phosphorylation of huntingtin at serine 13 and serine 16, suggested a potential role for GM1 in the treatment of HD.

20.4 Role of Glycolipids in the Link Between Parkinson's Disease and Gaucher Disease

A possible connection between Gaucher disease and Parkinson's disease has recently been suggested, although the molecular link between the two diseases is still somewhat obscure (Goldin 2010) (see also Chap. 19). The occurrence of Parkinson's disease in some type 1 (non-neuronopathic) Gaucher disease individuals

and their first degree relatives suggested *GBA1* mutations might be a genetic risk factor for idiopathic Parkinson's (Bultron et al. 2010). It has recently been shown that compared to the general population, there is an approximate 20-fold increase in lifetime risk of developing Parkinson's disease in patients with type 1 Gaucher disease (Bultron et al. 2010). Gaucher disease is caused by mutations in the *GBA1* gene that encodes the enzyme glucocerebrosidase which degrades glycosphingolipids to ceramide and glucose (Beutler and Grabowski 2001). *GBA1* mutations result in lysosomal accumulation of glucocerebroside (glucosylceramide). In type II Gaucher disease, increased levels of ganglioside GD3 have been reported in brain and in cerebrospinal fluid (Gornati et al. 2002); some studies have reported increases in expression of gangliosides GM2, GM3, GM1, and GD3 in the CNS in Gaucher disease while others have indicated either no change or decreases in gangliosides (Gonzalez-Sastre et al. 1974; Gornati et al. 2002; Conradi et al. 1984; Kaye et al. 1986). However, most of the reports of altered ganglioside expression were in association with type II or infantile forms of Gaucher disease. The extent to which CNS ganglioside expression is altered in type I Gaucher is unclear. However, ganglioside GM3 is reported to be strikingly elevated in plasma of type 1 Gaucher disease patients (Ghauharali-van der Vlugt et al. 2008).

A further link between Gaucher disease and Parkinson's disease is the presence of α-synuclein inclusions in brains of patients with type I Gaucher disease and Parkinsonism. Such patients also have Lewy body pathology and loss of substantia nigra dopaminergic neurons (Wong et al. 2004). Brain samples from patients with Gaucher disease or from Gaucher disease carriers with Parkinsonism all showed *GBA1* mutations and Lewy body pathology, with α-synuclein and glucocerebrosidase detected in Lewy body inclusions (Shachar et al. 2011; Goker-Alpan et al. 2010). It has also recently been shown that increased intracellular glucosylceramide (GlcCer) levels (GlcCer accumulates in affected tissues in Gaucher disease due to glucocerebrosidase deficiency) enhance the formation of toxic α-synuclein assemblies which may lead to neurodegeneration (Mazzulli et al. 2011).

20.5 Concluding Remarks

Although there have been tremendous advances in the understanding of the pathophysiology of numerous neurodegenerative disorders, there is still much that is not known about the mechanisms that initiate and drive neurodegeneration. This is particularly true in Parkinson's disease and Alzheimer's disease. Recent data though suggest that alterations in ganglioside biosynthesis and/or metabolism may be involved in numerous neurodegenerative disorders. Further research is now needed in order to better understand the nature of the changes in brain gangliosides in these disorders and to understand the extent to which these changes are either the cause or effect of neurodegenerative processes.

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