Review

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Gangliosides: glycosphingolipids essential for normal neural development and function

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Lipid rafts, sites of signal transduction, are enriched in glycosphingolipids (GSLs). Gangliosides, a class of GSLs found in greatest concentration in the grey matter of the brain, can affect neuronal function by modulating cell signaling. This review summarizes changes in ganglioside expression during brain development, the specific effects they induce, and makes observations about their possible role(s) in dementing diseases. Given that the average lifespan of individuals in many countries has increased, and that aging is accompanied by an increasing probability of dementia, understanding how changes in the GSL composition of lipid rafts may contribute to the cell biological basis of a specific dementing phenotype is an important area of study.

Gangliosides: part of the glycocalyx

The glycocalyx ('sweet husk') that surrounds many cells [1,2] provides the diversity of carbohydrate moieties needed for functions such as (i) cell differentiation, (ii) cell–cell interactions, and (iii) signal transduction. The carbohydrate moieties can also serve as antigenic determinants and as receptors for viruses, bacteria, and bacterial toxins. Cells in the central nervous system (CNS) express an abundance of cell surface glycosylated moieties including both proteins and lipids. The need for proteoglycans during neuronal development was established by the observation that reduced synthesis of heparin sulfate [3] resulted in disruption of neuronal migration (for more information about proteoglycans see [4]). This review focuses on the roles of a specific group of sialylated GSLs known as gangliosides (Figure 1A) that are essential for normal neural development and function. While present in most tissues including peripheral neurons, gangliosides are found in greatest concentration in the grey matter of the brain [5] and have a role in each of the functions mentioned above.

Despite Thudichum's introduction of the term sphingolipids in 1884 [6], decades elapsed before their structure and mode of synthesis was elucidated, and almost a century elapsed before the biological roles of these 'enigmatic' molecules began to be identified. Unlike glycoproteins, the carbohydrate portions of which can be found extending out as far as 1 μm from the cell surface [7], the carbohydrate portions of GSLs are held close to the surface by their ceramide moieties (Figure 1A). Synthesis of the ceramide component of gangliosides, GSLs identified by their carbohydrate composition and the presence of sialic acid, takes place in the endoplasmic reticulum, whereas that of the carbohydrate portion via the action of specific glycosyl transferases takes place in the Golgi (Figure 1B). Catabolism of the carbohydrate portion of gangliosides occurs in the lysosomes where removal of glycosyl residues is catalyzed by specific glycosidases. Both glycosyl transferases and hydrolases can be found in association with the plasma membrane where they can act to modify the carbohydrate composition ([8] for a review). For example, plasma membrane associated sialidase is able to catalyze hydrolysis of terminal sialosyl residues linked either α2–8 or α2–3 on a carbohydrate. In addition to variety in the carbohydrate portion of gangliosides, differences can be found in the sphingosine and fatty acid components comprising the ceramide portion. While the sphingosine and/or fatty acid chain length can vary in the ceramide portion of a ganglioside [9,10], stearic acid is the predominant acyl component. It is important to note that the hydrocarbon chain of sphingosine with its *trans* double bond between C4 and C5 and the presence of a saturated fatty acyl residue results in the hydrocarbon chains of gangliosides being able to pack more tightly together in a membrane than the *cis* double bonds found in unsaturated fatty acids associated with membrane phospholipids. These characteristics also enable cholesterol to interact well with them, with the result that gangliosides and other GSLs tend to associate with cholesterol as well as with particular proteins to form domains commonly referred to as lipid rafts ([11], a schematic is shown in Figure 2). These domains tend to be enriched in molecules involved in signal transduction, and in neurons have been shown to have an essential role in neuronal transmission [12]. In comparison to the polar head groups of phospholipids, the area occupied by the carbohydrate head groups of GSLs is greater and tends to introduce curvature into the membrane that contributes to their presence on its outer surface. Although the ceramide portion of a GSL can affect its function [13],

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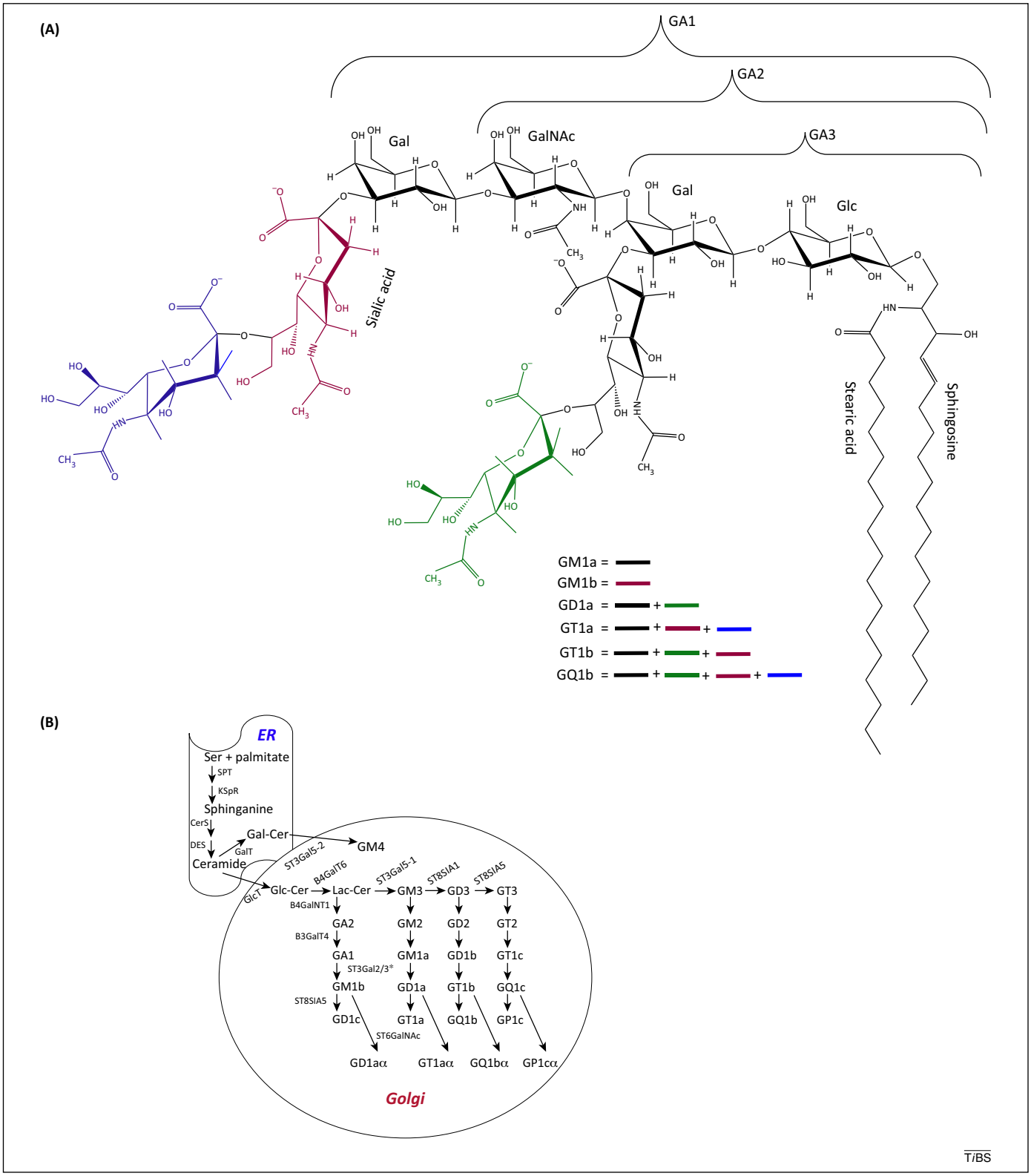

Figure 1. Representative ganglioside structures and synthetic pathways. The nomenclature used for ganglioside series gangliosides was developed by Svennerholm [21]. **(A)** Drawing of the moieties comprising many of the gangliosides found in brain. GA1, GA2, and GA3 indicate asialylated gangliosides while the legend indicates sugars found in several gangliosides present in brain. **(B)** Steps involved on the endoplasmic reticulum (ER) and in the Golgi during synthesis of many of the ganglioside species found in brain. Genes encoding enzymes responsible are listed for reactions that occur in the Golgi. α-Series gangliosides are synthesized from GD1a, GT1a, GQ1b, and GP1c by a sialyltransferase encoded by the *ST6GalNAC6* gene [85] termed CMP-NeuAc:β-*N*-acetylgalactosaminide α2,6-sialyltransferase, that catalyzes the transfer of sialic acid to the 6 position of GalNAc on GM1b, GD1a, and GT1b. For recent reviews on ganglioside biosynthesis see [86,87]. Enzymes indicated are: B3GalT4, UDP-galactose:GA2/GM2/GD2/GT2 β1–3 galactosyl transferase (ganglioside GA1, GM1a, GD1b, and GT1c synthase); B4GalNT1, UDP-GalNAc:LacCer/GM3/GD3/GT3 β1–4 *N*-acetylgalactosaminyl transferase (ganglioside GA2, GM2, D2, and T2 synthase); B4GalT6, UDP-galactose:glucosyceramide β1–4 galactosyl transferase (lactosylceramide synthase); CerS, ceramide synthase; DES, dihydroceramide desaturase; GalT, UDP-galactose:ceramide β1-1′-galactosyl transferase; GlcT, UGCG, UDP-glucose:ceramide β1-1′-glucosyl transferase; KSpR, 3-ketosphinganine reductase; SPT, serine-palmitoyl transferase; ST3Gal5, CMP-sialic acid:lactosylceramide α2–3 sialyltransferase (GM3 synthase); ST8SIA1, CMP-sialic acid:GM3 α-2,8-sialyltransferase (GD3 synthase); ST8SIA5, CMP-sialic acid:GD3 α-2,8-sialyltransferase (GT3 synthase). ST3Gal5-1 acts on GM3 only while ST3Gal5-2 can act on both GM3 and GM4 [88]; ST3Gal2/3 are needed in mice for synthesis of D1a and T1b [89].