Gangliosides of the Vertebrate Nervous System

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Abstract

Gangliosides, sialylated glycosphingolipids, found on all vertebrate cells and tissues, are major molecular determinants on the surfaces of vertebrate nerve cells. Composed of a sialylated glycan attached to a ceramide lipid, the same four structures—GM1, GD1a, GD1b, and GT1b—represent the vast majority (>90%) of gangliosides in the brains of all mammals and birds. Primarily found on the outer surface of the plasma membrane with their glycans facing outward, gangliosides associate laterally with each other, sphingomyelin, cholesterol, and select proteins in lipid rafts—the dynamic functional subdomains of the plasma membrane. The functions of gangliosides in the human nervous system are revealed by congenital mutations in ganglioside biosynthetic genes. Mutations in *ST3GAL5*, which codes for an enzyme early in brain ganglioside biosynthesis, result in an early-onset seizure disorder with profound motor and cognitive decay, whereas mutations in *B4GALNT1*, a gene encoding a later step, result in hereditary spastic paraplegia accompanied by intellectual deficits. The molecular functions of brain gangliosides include regulation of receptors in the same membrane via lateral (*cis*) associations and regulation of cell–cell recognition by *trans* interaction with ganglioside binding proteins on apposing cells. Gangliosides also affect the aggregation of Aβ (Alzheimer's disease) and α-synuclein (Parkinson's Disease). As analytical, biochemical, and genetic tools advance, research on gangliosides promises to reveal mechanisms of molecular control related to nerve and glial cell differentiation, neuronal excitability, axon outgrowth after nervous system injury, and protein folding in neurodegenerative diseases.

Introduction

Every cell in nature is endowed with a glycocalyx, a diverse coating of glycans, also referred to as glycoconjugates or complex carbohydrates [1]. The glycocalyx constitutes each cell's distinctive face to its environment, shaping cell surface biophysical properties and providing a biochemical signature that can be read by glycan recognition molecules [2–5]. In animals, the glycocalyx is composed of glycoproteins, glycolipids, and proteoglycans, the ratios of which vary greatly among cell types. Most of the cells of the vertebrate nervous system are unusual in that their glycocalyces are dominated by glycolipids and more specifically by glycosphingolipids consisting of glycans carried on a ceramide lipid embedded in the outer leaflet of the plasma membrane [6]. In nerve cells, these are primarily gangliosides (Figs. 1 and 2), glycosphingolipids with one or more sialic acid residue in their glycan structures [7,8]. Although gangliosides with various glycan structures are found in every vertebrate tissue, they are markedly more abundant in the nervous system. On average, each of the billions of nerve cells in the human brain has ~10 million cell surface gangliosides. Among mammals, the structures of the major brain gangliosides are well conserved, with the same four glycan structures (one pentasaccharide, two hexasaccharides, and one heptasaccharide) comprising the vast majority of brain gangliosides from mouse to man (Fig. 2). Advances in biochemistry, cell biology, and genetics are revealing the functions of these relatively abundant nerve cell surface molecules and their roles in human physiology and pathology.

This review presents the chemistry of the major mammalian nervous system gangliosides and the biophysical properties that endow them with distinctive behaviors at the plasma membrane. This is followed by review of some of the functions and

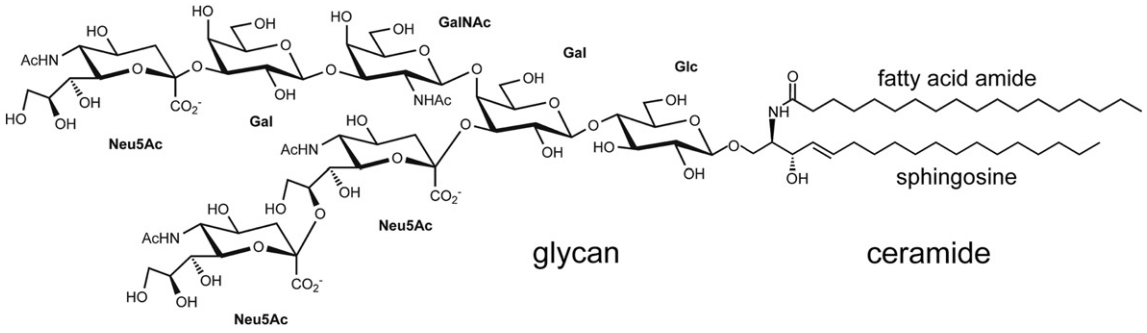

Fig. 1. Trisialoganglioside GT1b. The structure of the most complex of the four major mammalian brain gangliosides is shown. Other major brain gangliosides and their biosynthetic relationships are shown in Fig. 2.

pathophysiological roles of gangliosides, emphasizing major themes in recent research. Finally, technical advances that have opened new doors to the study of gangliosides and their functions are presented along with pressing technical challenges.

Chemistry and physics of mammalian nervous system gangliosides

Major ganglioside of mammalian nervous systems

Gangliosides are composed of a sialylated glycan attached to a ceramide lipid core (Fig. 1). The sialoglycan is typically composed of 3–8 saccharides, of which 1–4 are sialic acids, although gangliosides with glycan structures outside these ranges are well known [9]. The ceramide moiety is composed of sphingosine, a long chain 2-amino alcohol, in which the nitrogen is in amide linkage to a fatty acid. Gangliosides are found in all mammalian tissues, where variations in sialoglycans and in the lipid components of ceramide combine to generate hundreds of distinct ganglioside structures with a variety of functions that ranges from regulating receptor tyrosine kinases to directing cell–cell recognition [10]. Mammalian brain gangliosides, however, are quantitatively dominated by just four sialoglycan sequences (Fig. 2) and their ceramide lipid

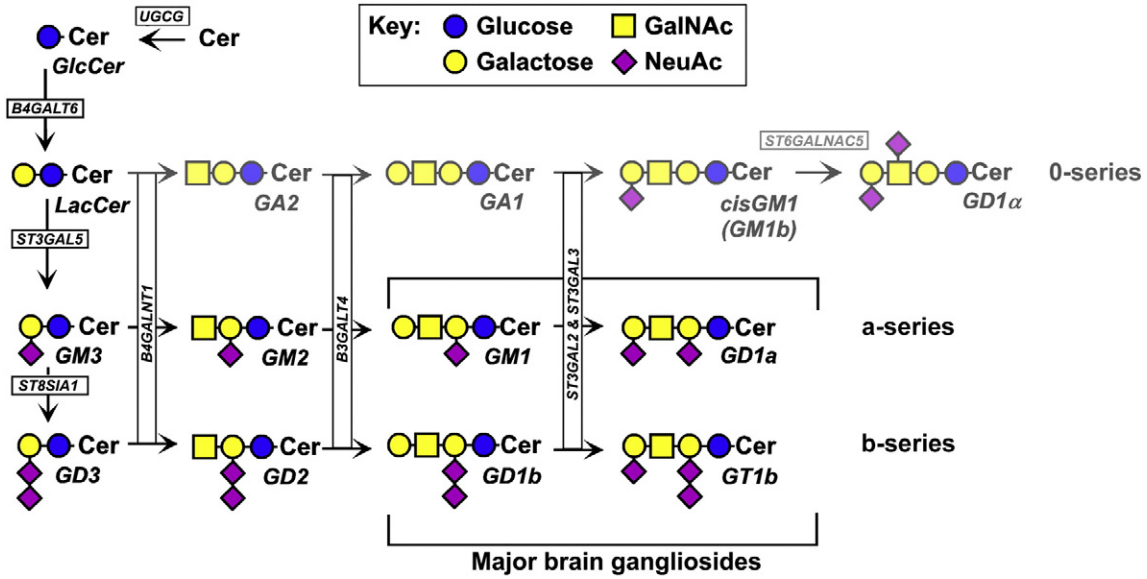

Fig. 2. Biosynthesis of mammalian brain gangliosides. The step-by-step enzymatic biosynthesis of the major brain gangliosides is shown, starting with addition of glucose in β-linkage to ceramide. Each enzyme transfers a single sugar from an activated sugar nucleotide donor (UDP-Glc, UDP-Gal, UDP-GalNAc, or CMP-Neu5Ac) to the end of the growing chain. Linkage positions of each sugar are not shown but are the same as for GT1b (Fig. 1), with the exception of GD1α, which has a sialic acid linked α2–6 to the GalNAc. Human genes encoding the enzymes responsible for each step are boxed. Note that some enzymes (e.g., *B4GALNT1*) act on multiple acceptors that vary in the number of sialic acids on the inner galactose. Ganglioside nomenclature is that of Svennerholm [111]. The glycan symbol nomenclature shown is widely accepted in the field [112].