Review

Ganglioside G\textsubscript{D3}: structure, cellular distribution, and possible function

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Keywords: gangliosides, reactive glia, gliomas, development, mutant mice, membrane permeability

Summary

Insight on the function of gangliosides can emerge from knowledge of their cellular distribution. In this paper we review the structure of ganglioside G\textsubscript{D3} and recent information on its cellular distribution. G\textsubscript{D3} appears to be enriched in a variety of neural cell types including: reactive glia, gliomas, undifferentiated neurons, Muller glia, and oligodendroglia. Because each of these cell types share an enhanced permeability to ions and metabolites or possess properties associated with enhanced permeability, we suggest that G\textsubscript{D3} is associated with enhanced membrane permeability. A possible function for G\textsubscript{D3} in membrane permeability has implications for other cellular events such as metabolism, growth and interactions.

Introduction

Gangliosides are a family of sialoglycosphingolipids that are present in the outer surface of plasma membranes. Although gangliosides are found in most vertebrate cells and tissues, they are most heavily concentrated in the central nervous system (CNS). The precise function of gangliosides in the CNS, however, is not yet clear. An understanding of ganglioside function may emerge through knowledge of their cellular distribution. Considerable information has recently accumulated on the distribution of ganglioside G\textsubscript{D3}. This information has implications for the possible function of this ganglioside.

Structure

Kuhn and Wiegant (1) first identified the structure of G\textsubscript{D3} in normal brain as that consisting of ceramide: glucose: galactose: N-acetylneuraminic acid with the molar ratios of 1:1:1:2, and assigned it the symbol G’ Lact. Ledeen et al. (2) later confirmed that this structure was identical to that for ganglioside G3A, which was elevated in the brain of a patient with subacute sclerosing leukoencephalitis. Hagberg et al. (3) also studied the structure of this ganglioside and designated it G\textsubscript{D3} (Figure 1). G\textsubscript{D3} often migrates as double bands on thin-layer chromatographic plates. (4-7) This is attributed to differences in fatty acid and long-chain base composition. (5,6) Ando and Yu (8) recently characterized the fatty acid and long-chain base composition of the upper and lower G\textsubscript{D3} bands isolated from normal human brain. The long chain base composition is similar in both bands, but the upper band contains a greater proportion of longer chain fatty acids (C20-C26) than the lower band, that contains mostly C18:0. Similar differences also occur between the double bands of G\textsubscript{M3}. (6, 8)

Compared to the hexosamine containing gangliosides (G\textsubscript{M1}, G\textsubscript{D1a}, G\textsubscript{T1b}, etc.), G\textsubscript{D3} and G\textsubscript{M3} contain less C18:0 fatty acid and more of the longer...
chain fatty acids. (8, 9) This phenomenon is seen for GD3 in retina (10, 11), optic nerve (5), and in subacute sclerosing leukoencephalitis brain (2). It is also noteworthy that the GD3 sphingosine base contains more d18:1 and less d20:1 than that of most hexosamine containing gangliosides (8, 11). Moreover, the sialosyltransferase that converts GM3 to GD3 appears to differ from the other sialosyltransferases in kinetic properties and in subcellular localization (12–15). These differences in lipophilic structure and biosynthesis between GD3 and the other gangliosides are indicative of differences in cellular localization. Further studies on the structure and metabolism of GD3 in normal and diseased CNS tissues should provide additional insight on its cellular distribution.

Enrichment of GD3 in reactive glia and gliomas

We found a strong correlation between reactive gliosis and increased GD3 content in the cerebells of various adult neurologial mouse mutants. GD3 is significantly elevated in the Purkinje cell degeneration (pcd/pcd), staggerer (sg/sg), and lurcher (Lc/+) mutants, but is not elevated in the weaver (wv/wv) mutant (7, 16–18). Because reactive gliosis occurs in the pcd/pcd and sg/sg mutants, but not in the wv/wv mutant (19–22), we suggested that GD3 is enriched in reactive glia and may serve as a marker for reactive gliosis. Since the Lc/+ and sg/sg mutants share similar histological abnormalities, we also suggested that reactive gliosis should occur in Lc/+ mice (17).

If GD3 is a reliable marker for reactive gliosis, then elevated amounts of GD3 should be found in all neurological disorders where reactive gliosis occurs. This notion is strongly supported from data in the literature (17). Increased amounts of GD3 and reactive gliosis occur together in multiple sclerosis (23, 24), subacute sclerosing leukoencephalitis (2, 25), kuru (26), Creutzfeld-Jakob disease (27–29), Alzheimer's disease (27), Huntington's disease (30), metachromatic leukodystrophy (31), congenital amaurotic idiocy (3), Krabbe's disease (32), and adrenoleukodystrophy (33, 34). Regardless of disease etiology, reactive gliosis is associated with elevated GD3. Since no exceptions to this general phenomenon have yet been found, GD3 can be considered a good marker for reactive gliosis in neurological disease.

In addition to reactive gliosis, elevated levels of GD3 are also found in gliomas of man and mouse (35–38). Although GD3 can be elevated in other brain tumor types (36–38), malignant astrocytomas generally contain the highest GD3 concentrations. Indeed, the degree of malignancy appears to be positively correlated with the content of GD3 (37, 38). GD3 can therefore be considered an important glioma-associated antigen. GD3 is also present in human melanoma and leukemic cells (39, 40, 41, 112), and its expression in cells transformed with human adenovirus gene E1 appears to be associated with tumorigenic activity (42). Taylor and Hogan (37) attributed the increase of GD3 in astrocytoma to the process of neoplastic transformation rather than to an increase in glial cell number. This is interesting since the astrocytic reaction in sg/sg mice, where GD3 is also significantly elevated, consists of an elaborate formation of sheet-like membraneous processes that are similar to structures occurring in neoplastic glial cells (20). It is therefore possible that GD3 has a common function in reactive and neoplastic cells.