Diet and Ganglioside Expression

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Gangliosides are series of glycosphingolipids containing sialic acids in the oligosaccharide portion in mammalian cells. Gangliosides are a component of cellular membranes and play roles in modulating membrane function and the activity of membrane proteins. Abnormal expression and metabolism of gangliosides lead to the onset of several conditions in humans, such as neurologic diseases, diabetes, and cancer. A number of studies have been carried out to date to investigate the role of gangliosides in these diseases, and the effect of diet on tissue expression of gangliosides has recently become a topic of interest in this field. As gangliosides are degraded in the intestinal tract, ingested food-derived gangliosides are not directly absorbed into tissues in vivo, but the degradation products can be absorbed and affect ganglioside expression in the tissues. Recent studies have also shown that the expression of gangliosides in tissue cells can be indirectly induced by controlling the expression of ganglioside metabolism-related genes via the diet. These results indicate that dietary control can regulate the expression levels of gangliosides in tissues, which is expected to play a role in preventing and treating ganglioside-related diseases.

Keywords: ganglioside ; glycosphingolipid ; ketogenic diet ; low-carbohydrate diet ; glycosyltransferase gene

1. Introduction

A number of studies are currently underway examining the effect of diet on the expression level of tissue gangliosides. Although the details remain to be fully elucidated, recent progress has revealed new information regarding the effects of diet on ganglioside dynamics, metabolism, and induction. Cellular responses to nutrients and stress have also been identified as factors involved in the regulation of tissue ganglioside expression. This section describes these findings.

2. Gangliosides in Foods

Gangliosides are found in animal-derived foods such as meat, fish, egg yolk, and dairy products. The composition of molecular species of gangliosides in these foods are listed in Table 1. Dairy products primarily contain GD3 [1], but meat and fish contain GM3 [2]. These foods also contain complex gangliosides as minor components. Complex gangliosides are major lipid components in animal brains used as food in certain cultures.

Table 1. Ganglioside components in foods.

Food		Major (Minor) Ganglioside Component	Reference
Meat	Beef	GM3 (GD3, GD1a)	[2]
	Pork	GM3 (GD3, GD1a, GD1b)	[2]
	Chicken breast	GM3 (GD3)	[2]
	Chicken thigh	GM3 (GD3, GD1a, GD1b)	[2]

Fish	King salmon	GM3 (GD3)	[2]
	Snapper	GM3 (GD3, GD1a, GD1b)	[2]
	Island mackerel	GM3 (GD3, GD1a, GD1b)	[2]
	Turbot	GM3 (GD3, GD1a, GD1b, GT1b)	[2]
	Tuna	n.d.	[3]
Egg yolk		n.d.	[3]
Human breast milk	Early stage	GD3	[4][5]
	Late stage	GM3	[4][5]
	All stages	(GM1 and others)	[5][6][7]
Dairy products	Bovine milk	GD3 (GM3)	[8]
	Bovine butter	GD3 (GM3)	[1]
	Yogurt	n.d.	[3]
	Infant formula	GD3 (GM3)	[8][9]
	Cheddar cheese	n.d.	[3]
	Whey	GD3 (GM3)	[9]
LCKD (Bio-Serv F3666)		GD3 (GM3)	[10]

n.d., not determined; LCKD, low-carbohydrate ketogenic diet.

GD3 is the major ganglioside in human breast milk during the early lactation stage, whereas GM3 becomes the major ganglioside in later stages [4][5]. Some complex gangliosides are also found in breast milk [5][6][7][8]. Bovine milk contains GD3 as the major ganglioside, and therefore, formula prepared using bovine milk also contains this ganglioside [8]. Gangliosides can remain stable in breast milk for long periods at several storage temperatures [11]. Pasteurization has almost no effect on the stability of gangliosides in breast milk.

Plants and fungi contain almost no sialic acid and therefore do not contain gangliosides. However, edible plants such as soybean, corn, rice, wheat, and konjac (*Amorphophallus konjac*, K. Koch) are rich in glucosylceramide [12][13], a ganglioside precursor. Although not used as a food source, marine sponge (*Agelas mauritianus*) contains a neutral glycosphingolipid, αGalCer, which activates innate immune responses in mammals [14].

3. Digestion and Absorption of Gangliosides in Foods

Gangliosides contained in foods are degraded in the intestinal tract (Figure 1), and the remaining intact structures are not taken up into the blood and lymph fluid. However, the products of ganglioside degradation, such as saccharides and lipids, are supplied to the tissues, where they promote the biosynthesis of gangliosides. In mammals, gangliosides are first degraded in the small intestine by sialidase/neuraminidase, which removes the sialic acid residues [15], and then sequentially degraded into saccharides and ceramides by glycosylceramidase present in the small intestinal mucosa [16].

Ceramides are further degraded into sphingoid bases and free fatty acids by neutral ceramidase [17][18]. These degradation products (saccharides and lipids) are absorbed by small intestinal epithelial cells and then partially re-synthesized into glycosylceramides [16][19]. Gangliosides are thought to be re-synthesized only in tissue cells that express enzymes involved in ganglioside synthesis. The results of these studies indicate that saccharides and lipids derived from gangliosides induce ganglioside expression in tissues. The sialic acid *N*-glycolylneuraminic acid (Neu5Gc), which is found in edible animals but not in humans, is abundant in red meat and dairy products [20]. Consumption of these foods supplies tissue cells with Neu5Gc and results in the synthesis of ganglioside species containing Neu5Gc, which are known to be highly expressed in cancer cells [21].

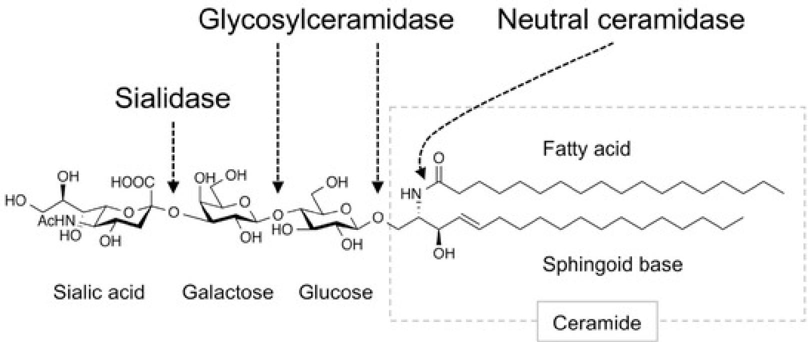

Figure 1. Ganglioside-degradation enzymes in the intestinal tract. Digestive enzymes that degrade gangliosides in the mammalian intestinal tract are shown. Arrows indicate linkage regions in the ganglioside degraded by these enzymes. Figure shows GM3 as an example ganglioside.

Breast milk is a rich source of oligosaccharides containing sialic acid, and the primary oligosaccharide, sialyl lactose, has the same structure as the oligosaccharide of GM3 [22][23]. Infants raised on breast milk have a significantly higher sialic acid content in the gangliosides and glycoproteins in the frontal cortex of the brain than infants fed formula [22]. Sialyl lactose has isomers that exhibit different sialic acid binding patterns, and a model experiment in which pigs were fed these isomers showed that each isomer increases the sialic acid content of gangliosides in a similar manner in several brain regions [23]. These results indicate that the degradation products of sialyl lactose promote ganglioside synthesis in brain tissues. Several animal experiments have shown that a high sialic acid content in gangliosides in the brain is associated with neuronal development, based on the formation and stabilization of functional synapses and neural circuits, leading to improved cognitive function, memory formation, and learning ability [24].

4. Indirect Effects of Dietary Components on Ganglioside Expression

Several studies have found that ganglioside expression in tissues is affected by various nutrient deficiencies or foods that do not provide components for ganglioside synthesis. A study investigating the effects of undernutrition in neonatal rats induced by feeding the mothers a low-protein diet during lactation showed a marked decrease in brain ganglioside content, along with decreases in body and brain weight [25]. Ganglioside expression in neonatal rat brain is also affected by thiamine and vitamin A deficiency [26]. Chronic consumption of ethanol also reportedly affects the expression of gangliosides in the rat brain [27]. Vitamin K deficiency is known to be associated with cognitive and behavioral perturbations in rats, as well as changes in the expression of gangliosides in the hippocampus, striatal striatum, and prefrontal cortex hippocampus in the rat brain [28]. Another study reported that a high-fat diet decreases glycosphingolipid levels in mouse liver [29], whereas our previous study revealed that ganglioside content in the liver increases in mice fed a high-fat, very-low-carbohydrate ketogenic diet (LCKD) [30][31].

5. Dietary Induction of Tissue Ganglioside Expression Via Transcriptional Regulation of Ganglioside Metabolism-Related Genes

Indirect changes in the expression of gangliosides induced by the diet are suggestive of specific changes in the metabolic pathways of ganglioside synthesis and degradation. A number of genes related to ganglioside biosynthesis and metabolism have been identified in recent years, and it has become clear that the expression of gangliosides in tissue cells is regulated by the expression of specific genes, suggesting that transcriptional regulation of ganglioside metabolism-related genes could be targeted by dietary factors that affect tissue ganglioside expression. The molecular species of ganglioside expressed in each type of tissue cell is controlled primarily by the corresponding glycosyltransferase gene.

Analyses of the properties of these genes using cultured cells have revealed several targets for modulating ganglioside metabolism, such as transcription factors, signal transduction, and stress responses; controlling these targets thus regulates the expression of gangliosides in cells [32][33].

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