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Relationship Between Ganglioside Metabolism and the Development of Metabolic Syndrome and its Complications

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Gangliosides are important biological molecules, performing functions as key regulators of many physiological processes on cellular, tissue, organ and organism level. These substances have shown a large structural heterogeneity, mainly in result from differences in number, identity, linkage and anomeric configuration of the carbohydrate residues, as well as from some structural differences. Relationship between the values of different gangliosides, the titers of specific auto-antibodies to each one ganglioside and the pathology of multi-factor socially important diseases and disorders has been underlined. These bio-molecules, as well as the interactions with their participation, or even lack of gangliosides in separate cases, are underlining the final clinical picture. Based on the deviation levels of ganglioside GM3 in some abnormalities of the glucose and lipid metabolism, the serum levels of GM3 are characterized as a marker for the severity of metabolic syndrome.

Key words: gangliosides, cascade regulatory pathways, socially important diseases and disorders, metabolic syndrome.

Introduction

Gangliosides are complex acidic glycosphingolipids, containing one or more sugar residues, attached to a sphingolipid moiety, usually to a ceramide, but in rare cases also to a sphingoid base [13]. A large structural heterogeneity has been found to result from differences in number, identity, linkage and anomeric configuration of the carbohydrate residues, as well as from some structural differences, particularly within the hydrophobic part. These molecules have been characterized as key regulators of many physiological processes on cellular, tissue, organ and organism level. Although the structures of gangliosides have been assigned to only a few series with a common carbohydrate core, their structural variety and the complex pattern are challenges for their elucidation and quantification by mass spectrometric techniques [8]. The alterations in the metabolism of gangliosides have been determined as one of the earliest changes, associated with the diabetic pathology [9, 13, 43]. Besides in free form, each ganglioside has been found to exist in various bounded forms with different bio-molecules, depending of the

respective functions, in which it participates [4, 7, 25-27, 52, 59]. In addition, cross-reactions of specific antibodies to each ganglioside with other biological molecules have also been suggested. Furthermore, these studies show a possibility for production of immunoglobulins/antibodies by non-lymphoid types of cells, tissues and organs [18, 37]. The control of the activity of the so produced antibodies is very important. Namely gangliosides have been proved also as small molecules, which provide such control.

Gangliosides, Obesity and Metabolic Syndrome. Ganglioside GM3 has been found to function as a physiological regulatory factor of the balance between homeostatic and pathological states in adipocytes by modulating insulin signaling in lipid rafts [35]. In order to counteract obesity-related metabolic disorders, the importance of therapies targeting GM3 biosynthesis has been highlighted [26]. The role of this ganglioside in mediation of obesity-induced perturbations in metabolic function, including impaired insulin action, has been particularly underlined. A probability of development of insulin resistance in increased levels of GM3 in the visceral adipose tissue of obese humans has been proposed [58]. In this connection, therapeutic strategies, aimed at targeting biosynthesis of this ganglioside for counteraction to obesity-induced metabolic perturbations, as well as of other manifestations of the metabolic syndrome, have been suggested. Several candidate-proteins, which may be involved in the generation of NeuGc (N-glycolyl) GM3 have been revealed, particularly GM3 synthase and subunit B of respiratory complex II (SDHB) [5]. Significant changes in quantity and quality of gangliosides (particularly GM3) in each stage of differentiation of mouse C2C12 myoblasts have been found [15]. According to other studies, induced down-regulation of enzyme NEU3 sialidase in the same mouse cells has totally inhibited the capability of these cells to differentiate by increasing the GM3 level above a critical point [2, 19]. The authors have also proposed that influence on the functions of epidermal growth factor receptor (EGFR) could probably lead to activated responsiveness of the myoblasts to apoptotic stimuli. GM3, as well as the enzymes, involved in its metabolism, have been characterized as the best "candidates", correlating with a number of metabolic disease risk factors as autotaxin, LDL-c and homeostatic model assessment insulin resistance [6, 55]. These data have been supported by the established metabolic abnormalities in *Rhesus macaques*, subjected to high-fat and high-fructose Western-style diet [6]. Based on the deviation levels of GM3 in some abnormalities of the glucose and lipid metabolism, the serum levels of GM3 are characterized as a marker for the severity of metabolic syndrome [44]. In this aspect, the role of GM3 as a negative regulator of insulin signaling has confirmed it as a potential therapeutic target in type II *Diabetes mellitus* [60]. The role of GM3 in mediating obesity-induced perturbations in metabolic function, including impaired insulin action has been proved [26].

***Gangliosides and Diabetes*.** The synthesis of gangliosides has been suggested as an important pathway for glucose utilization in early stages of some diabetic complications as diabetic nephropathy [38]. These molecules have also been proved as mediators of the insulin resistance. Reports about correlation of alterations in their levels, types, distribution and metabolism with diabetes, including its autoimmune form, have also been obtained [28, 31, 32, 54]. In this way, gangliosides have been suggested as antigens, playing a role of targets for specific auto-antibodies in diabetic patients [14]. a-Series gangliosides are mediators of the effects of advanced glycation end products (AGEs). Their participation in some pathological and degenerative consequences of

diabetes, as diabetic retinopathy and diabetic nephropathy, has been suggested [28]. AGEs have also been proposed to be involved in the micro-vascular alterations in some diabetic complications as diabetic retinopathy [36]. In non-obese diabetic (NOD) mice increased titers of the islet cell antibodies (ICA) have been observed, and the distribution of beta-cells has been found as associated with a significant decrease in the amounts of gangliosides GM1 and GM2 in their pancreas, unlike of C57BL/10 mice [11]. Significant correlation of the increased production of plasma ceramides with the decline in insulin sensitivity has been established [6]. In this aspect, particularly the increased values of ganglioside GM3 have been supposed to participate in the development of the insulin resistance and in this way – in the pathogenesis of diabetes [20, 23, 26, 51]. Affected serum GM3 levels have been established in abnormalities in the glucose and lipid metabolism [45]. Additionally, the depletion of the same ganglioside, as well as of enzymes, responsible for its synthesis, has been found to protect against different pathological and degenerative consequences of diabetes [30, 41, 57]. In this relation, GM3 has been determined as a pathophysiological mediator in the development of diabetic nephropathy [38, 56]. On the other hand, ganglioside GM1 has been determined as an attractive target for detection, prevention and treatment of insulin resistance, of subsequent diabetes development, as well as of related complications, probably by abundant activity of this ganglioside on the surface of endothelial cells [44, 66]. In this regard, a possibility for improvement of both insulin sensitivity and glucose homeostasis by glycosphingolipid synthesis inhibition has been suggested as a novel therapeutic approach for the treatment of type 2 diabetes [67]. Based on the deviation levels of GM3 in some abnormalities of the glucose and lipid metabolism, the serum levels of GM3 are characterized as a marker for the severity of metabolic syndrome [45]. Additionally, the role of GM1 in the activation of mediated by NO vasodilatation has been proved [13]. Taking in consideration the established nature of tyrosine kinase substrate p58/p53 and the insulin receptor as components of central nervous system (CNS) synapses, a role of the insulin signaling at these synapses has been proved [1]. Increased risk for development of type 2 diabetes in patients with *Alzheimer's* disease has also been assessed, caused by general mechanism, underlining loss of β-cells and brain cells, respectively [21].

Gangliosides and Neurodegenerative Complications. The influence of gangliosides, but also the correlation of their levels, distribution and metabolism, on the development, structure and functions of the neural system and brain, have been proved [10, 61]. Due to their amphiphilic nature, gangliosides have been found localized to the cellular membranes, and many of their functions in health and disease have been established to result from both membrane reorganization and lipid interaction with proteins within the membrane structures [10]. The injuries in the levels, synthesis, degradation and metabolism of gangliosides have been proved as main signs of the early development of the neuro-degenerative diseases and disorders, as well as for understanding of the pathological mechanisms, underlining these processes [3, 17, 59]. Brain ganglioside content and composition, but also the metabolism of these bio-molecules, have been found to be altered in *Alzheimer's* disease. Changes in the neuron membrane physico-chemical properties have been proposed as a consequence of primary pathology, which might also be involved in the early pathogenesis of this neuro-degenerative disorder through documented effects on proteolytic processing and amyloid aggregation of

amyloid-precursor protein (APP). In *Parkinson's* and *Huntington's* diseases, significant alterations in the levels, distribution and metabolic pathways of gangliosides have also been established [10]. These results could be confirmed by data for the proved role of ganglioside GM1 in the promotion of neurite outgrowth signal [19, 59, 64]. Binding of GM1 to laminin-1 leads to activation of NGF-TrkA signaling pathway. This mechanism has been supposed as underlining the processes, described above. The role of auto-antibodies to gangliosides in the development of many neuropathies has also been proved [27, 54]. Furthermore, most of the anti-ganglioside antibodies have shown anti-sulfatide reactivity distinct from the other known antibodies, which has been proposed as one of the factors in demyelinating neuropathies development [29]. The appearance of anti-sulfatide, but also of anti-GM1 and anti-GM2 IgM auto-antibodies have been associated with immune-mediated neuropathies in younger age [24]. In many cases, the role of GM1 in modulation of Trk and Erk kinases phosphorylation and activity in the brain has been established [12, 33]. Namely the proved tight association of GM1 with Trk has determined this ganglioside as a specific endogenous activator of the neuronal growth factor (NGF) receptor function [34]. A novel mechanism of neuronal apoptosis, mediated by GM1 accumulation has also been proposed [53]. Participation of ganglioside GM3 as a mediator in the neuronal cell death has also been proved [50].

Gangliosides and Vascular Complications. Gangliosides have been established to be primarily but not exclusively, localized in the outer leaflets of plasma membranes of the cells, and they have been characterized as integral components of cell surface microdomains with sphingomyelin and cholesterol, from which they participate in cell-to-cell recognition, adhesion and signal transduction [62]. In many cases, alterations in the levels of this ganglioside GM3, as well as in its metabolism, have been associated with obesity, type 2 diabetes, metabolic syndrome, atherosclerosis and hypertension [54]. A correlation of the increased cellular levels of GM3 in monocytes and lymphocytes in atherosclerosis with cell activation, facilitating their adhesion to endothelial cells and penetration into the *tunica intima*, has been suggested [16]. In this connection, GM3 has been suggested to be significantly correlated with the thickness of *tunica intima* and *tunica media*, which is often used for detection of atherosclerotic disease, as well as with many connected with the same disorder risk factors as LDL and insulin resistance [55]. Biologically-relevant GM1 concentrations have been found to lead to submicron-sized domains in a cholesterol-rich liquid-ordered phase [65]. Eventual existence of small ganglioside-rich microdomain within a larger ordered domain in both natural and model membranes has been proposed [62, 63].

Gangliosides and Cholestatic Complications. Most of the normal serum gangliosides have been found to be synthesized in the liver [46, 48]. However, this anatomic organ has also been characterized as the main source of elevated levels of serum gangliosides in many liver diseases and disorders [46, 47]. Changes in the synthesis and/or distribution of gangliosides within the hepatocytes have been established due to estrogen-induced cholestasis, probably as a consequence of oxidative stress, but also the detergent properties of highly-concentrated bile acids [40, 49]. In this way, the authors have proposed a general mechanism of hepatoprotection by the gangliosides. These data have been confirmed by the observed significant changes in the distribution and synthesis of liver gangliosides, accompanying the cholestasis, in particular its obstructive form. Similar effects have been observed in the livers

of rats with experimentally-induced diabetes by treatment with Streptozotocin [43]. Also, changes in the molecular sub-species of ganglioside GM3 in human liver during the aging have been noted [39, 42]. Enhanced production of ganglioside GM1 at the sinusoidal membrane has been proposed to be due to re-distribution of cellular GM1 at limited biosynthesis and thus, could be responsible for protection of hepatocytes against harmful effects of bile acids, accumulated during the process of cholestasis [22]. In liver diseases deviations in the total concentration, pattern and distribution of serum gangliosides to different lipoprotein classes have been supposed [46]. These changes are probably due to qualitative and quantitative alterations in biosynthesis of gangliosides and secretion into the circulation (in cirrhosis), and lipoprotein metabolism alterations following cholestasis.

Conclusion

Gangliosides perform important role as key regulators in many physiological processes on cellular, tissue, organ and organism level. Disbalance in their values, as well as of different molecules, participating in their metabolism by cascade regulatory pathways, has been implicated in the pathology of multi-factor socially important diseases and disorders. On the other hand, the deviations, connected with the type, values and distribution of respective ganglioside and/or of various molecules, participating in its metabolism, could lead to development of various diseases and disorders. These molecules and the interactions between them or even lack of gangliosides in separate cases could lead to the final clinical picture. In this way, monitoring of the quantity and quality changes of gangliosides could be usable for determination the eventual risk for the metabolic syndrome development and expression.

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