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Research Article

Production of anti-GM3, anti-GM1, and anti-GD1A antibodies by non-lymphoid cells, tissues, and organs

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Abstract

Gangliosides are acidic glycosphingolipids localized mainly on the outer membrane layer of the membranous cell structures. These molecules participate in important mechanisms at molecular, cellular, tissue, organ, and organism levels. It has been proven that gangliosides play a role as regulators of various biological processes but also as markers in a number of multifactor pathologies. In this regard, the present study determined the titers of the GM3, GM1, and GD1a gangliosides, as well as the titers of IgG-class antibodies against each of them by enzyme-linked immunosorbent assay (ELISA), in several different anatomic organs: brain, pancreas, myocardium, liver, and small intestine from rodents. A total extract (control sample) containing the complete set of molecules is prepared from each isolated anatomic organ. An equivalent amount of the extract is passed through a GSH-agarose column in order to select the molecules from each organ possessing affinity to the reduced form of glutathione tripeptide (GSH). GSH is known as an antioxidant, immunomodulator, cardioprotector, neuroprotector, hepatoprotector, anticancer, and antiaging agent. As a whole, significantly lower titers of the three gangliosides and the antibodies to them are reported in the myocardium and liver samples compared to the brain and pancreas samples. Taking into account that the myocardium and liver are the organs known with the highest content of GSH, the obtained results can be explained by the possibly high content of free and/or newly synthesized GSH in them, which does not participate in intermolecular interactions compared to the other investigated organs. Complete absence of each of the three tested gangliosides or of antibodies against them at certain dilutions of the small intestine samples, as well as the highest titers of the same parameters compared to the corresponding samples from the other organs of each of the gangliosides or of the specific antibodies at other dilutions, is observed. One of the explanations for those peculiarities is associated with the presence of the intestinal microflora, including the influence of intestinal bacteria neuraminidases (sialidases). The presented data also show a possibility of antibodies/immunoglobulins production by non-lymphoid cells, tissues, and organs in suitable conditions. Since the immunoglobulins thus produced reside outside the germinal centers of the specialized lymphoid tissues and organs, regulation of their production and functions by interactions with small ions and/or molecules is also important. Gangliosides are namely such small molecules. Special attention is paid to intermolecular interactions involving the listed gangliosides and GSH. The main objective is related to understanding the mechanisms underlying the interaction between the individual organs and systems in the body.

Keywords

gangliosides, anti-ganglioside antibodies, intermolecular interactions, non-lymphoid cells, tissues and organs

Introduction

A number of tumor-suppressor proteins are important in preventing the development of malignant processes, as well as in the control of diabetes and a number of neurodegenerative disorders. The glutathione tripeptide, and more specifically, its reduced form (GSH), is known for its antitumor, cardioprotective, neuroprotective, immunomodulatory, antioxidant, and antiaging effects (Jahren-Hodje et al. 1997). On the other hand, gangliosides are complex acidic glycosphingolipids known as regulators of various biological processes at cellular, tissue, organ, and organism levels (Xu et al. 2010; Lucki and Sewer 2012). They are mainly localized on the outer membrane layer of the membranous cell structures. Gangliosides represent integrated components of cell surface microdomains composed of sphingomyelin and cholesterol, which participate in various key processes such as intercellular interactions, adhesion, and signal transduction (Yu et al. 2011). A number of variations in the titers, types, ratios, and distribution of these molecules, as well as of the antibodies against them, are found during the organism's development and aging processes. Variations in these parameters have also been established between the individual cells, tissues, organs, and organisms, between healthy and sick individuals, in different diseases, including in individual cases with the same clinical picture.

Recently, ganglioside GM3 has been identified as a mediator in diabetes, as well as in a number of complications in different cases of this disease (Menichella et al. 2016). A relationship has been suggested between the development of microvascular complications, increased levels of glycation end products, and increased levels of the GM3-synthetase enzyme in patients with diabetes mellitus (Masson et al. 2005; Wang et al. 2014). In this regard, the accumulation of GM3 ganglioside has been suggested as one of the main causes for the disruption of signaling interactions also involving insulin, which often leads to the emergence of insulin resistance (Tagami et al. 2002; Kabayama et al. 2005; Kabayama et al. 2007).

The neuroprotective role of GM1 ganglioside in the neuronal cell nucleus has been proven (Rong et al. 2013), including after ischemic stroke. In the latter case, the importance of this ganglioside has been proposed to suppress the subsequent neuronal autophagy (Li et al. 2016). A link has been established in the mechanism of this protection to the transport of calcium ions between the interior of the cell nucleus and the nuclear membrane (Xie et al. 2002). The ability of the GM1 ganglioside to interact with the Trk protein defines the role of GM1 as a specific endogenous activator of the neuron growth factor receptor (Mutoh et al. 1995).

The role of GD1a ganglioside in counteracting the suppressive effect of aggregated fibronectin has been proven in patients with multiple sclerosis (MS) upon oligodendrocyte maturation through activation of the PKA molecule-dependent signaling mechanism (Qin et al. 2017). Significantly increased values of the GM1/GD1a and GM1/GT1b ratios have been found in aging adult rodents compared to young test rodents (Aydin et al. 2001). One of the explanations for those observations are age-related changes in the titers of different gangliosides, but also in the ratios between them (Caughlin et al. 2017).

The main objective of the present study is aimed at more in-depth research on the influence of GM3, GM1, and GD1a gangliosides, as well as of the antibodies against them, in various processes in individual tissues and organs. For this purpose, experimental *in vivo* models of several anatomic organs from experimental rodents were developed. Special attention is paid to the intermolecular interactions in which both the three listed gangliosides and the GSH tripeptide are involved. The main idea is related to understanding the mechanisms underlying the interactions between individual organs and systems in the organism.

Materials and methods

Extracts are prepared from several different anatomic organs of experimental rodents: brain, pancreas, myocardium, liver, and small intestine. The extract from each organ is divided into two equal parts. One of them represented a total extract of the respective anatomic organ, containing the complete set of molecules (control sample). The other part of the extract is passed through a GSH-agarose column in order to select the molecules in the respective organ possessing affinity to GSH.

The presence and titers of GM3, GM1, and GD1a gangliosides, as well as of specific IgG-antibodies against them, in the samples of the investigated anatomic organs, are determined by applying enzyme-linked immunosorbent assay (ELISA). In summary, a solution of 1000 ng of each tested ganglioside (dry matter, Sigma) is added drop by drop in 100 ml of methanol in a 96-well plate. After air drying, the wells are blocked with a 1% solution of bovine serum albumin (BSA - Sigma) in phosphate buffer solution (PBS - Sigma) for 1 hour. After 6-times washing of the plates with PBS (Sigma), 100 μL of the samples from each anatomic organ, diluted 1:40 to 1:400 in PBS (Sigma), are placed drop by drop into each well. After overnight incubation and 6-times washing with PBS (Sigma), the samples are incubated in a 1% solution

of BSA in PBS (Sigma), after which they are treated with a solution of peroxidase-bound goat anti-IgG antibody (Bul Bio Ltd., NCIPD, Sofia) and are incubated at 4 °C. After 6-times washing with PBS (Sigma), the reaction is performed by adding a solution of 15 mM orthophenylene in 0.1M (0.2 M CH_3COONa/sodium acetate buffer 0.2 M CH_3COOH; pH 5.0) in the presence of 0.015% H_2O_2 at 20 °C. After 30 minutes, the reaction is stopped by adding 50 µL of 1N H_2SO_4. Optical density (OD) is read spectrophotometrically at a wavelength of 490 nm on an ELISA-reader (TECAN TM, Sunrise, Austria). Non-specifically bound antibodies (OD values not containing specific molecules for the respective tested sample) are eliminated. The results are considered statistically significant at OD 2 ± SD (standard deviation) values compared to controls, at $p < 0.001$ and $p < 0.005$. For maximum reliability, the described procedure is repeated three times.

Results

In brain extract samples, higher titers of GM3 ganglioside compared to titers of anti-GM3 antibodies are established in all cases (Fig. 1). This trend is observed in the total extract (Fig. 1A) and in the sample containing molecules with affinity for GSH (Fig. 1B). However, the differences are not statistically significant. A similar pattern is observed for the same samples from pancreatic extract, but in that case statistically significant differences are observed (Fig. 1C, D). Only at 1:400 dilution in the total pancreas extract is the titer of anti-GM3 antibodies (Fig. 1D) significantly higher than the titer of GM3 ganglioside (Fig. 1C). In the total myocardium extract, at all dilutions, significantly higher titers of the GM3 ganglioside are established compared to those of the anti-GM3 antibodies (Fig. 1E). An opposite trend is observed in the myocardium extract sample containing molecules with affinity for GSH, where significantly higher anti-GM3 antibody titers are observed compared to GM3 ganglioside titers (Fig. 1F). Only at a dilution of 1:40 in both the total liver extract and the sample from the same organ containing molecules with affinity for GSH are significantly higher anti-GM3 antibody titers available compared to GM3 ganglioside titers (Fig. 1G). Despite being in minimal amounts, anti-GM3 antibodies are detected in the total liver extract at dilutions 1:200 and 1:400, but no presence of the GM3 ganglioside is assessed. At dilution 1:100 of the total extract from the same organ, neither GM3 ganglioside nor anti-GM3 antibodies are detected (Fig. 1G).

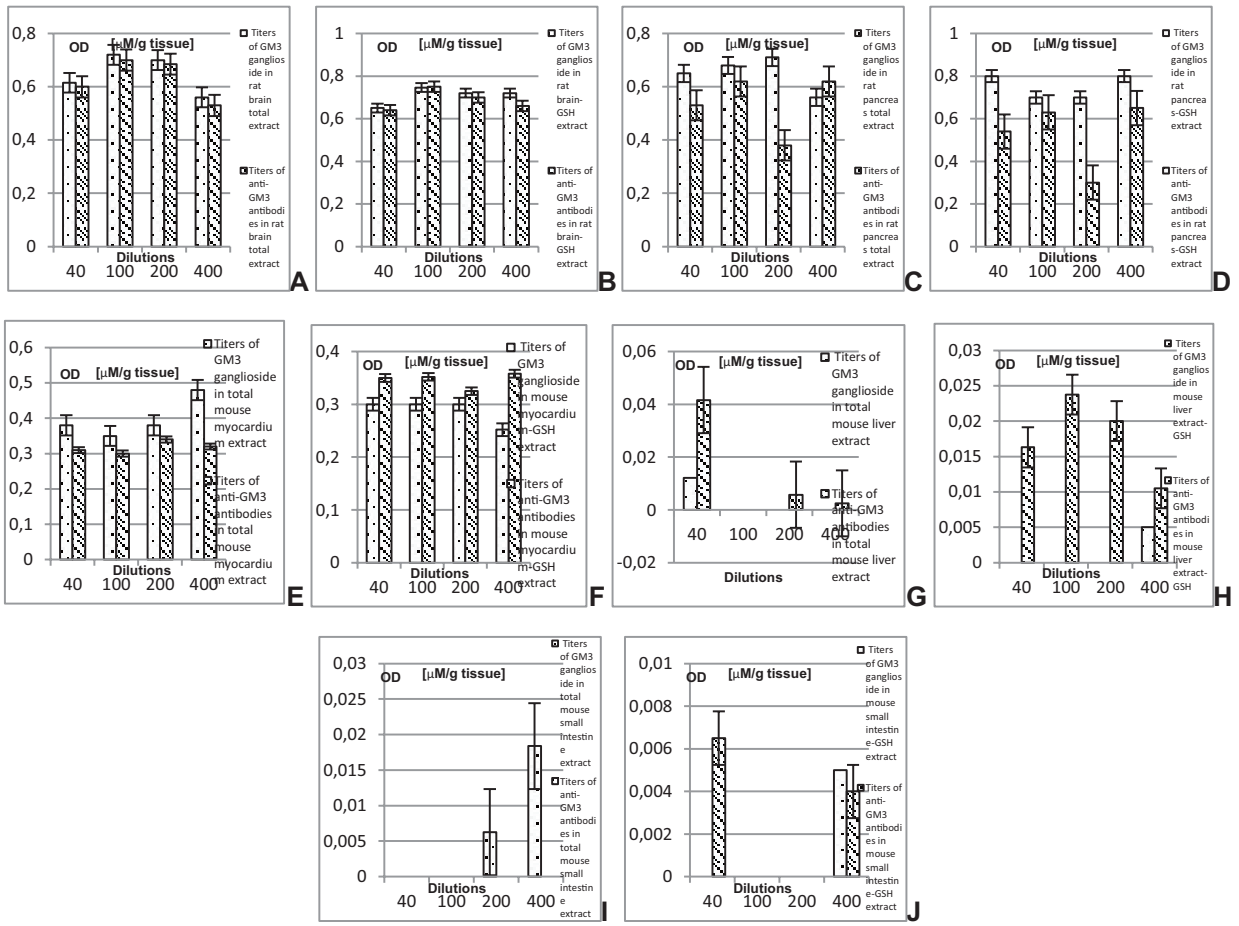

Figure 1. Titers of GM3 ganglioside and anti-GM3 antibodies in extracts from rodent brain (**A, B**), rodent pancreas (**C, D**), rodent myocardium (**E, F**), rodent liver (**G, H**), rodent small intestine (**I, J**); **A, C, E, G, I**—control samples; **B, D, F, H, J**—containing molecules possessing affinity to tripeptide GSH.

Regarding the liver extract sample containing molecules with affinity for GSH, at all dilutions (from 1:40 to 1:400), the presence of anti-GM3 antibodies is observed, but the GM3 ganglioside is absent. Only at a dilution of 1:200, an insignificant presence of the ganglioside is detected (Fig. 1H). In the total small intestine extract, only dilutions 1:200 and 1:400 show the presence of anti-GM3 antibodies, but GM3 ganglioside is absent in both of them (Fig. 1I). In the small intestine extract sample containing molecules with affinity to GSH, only at a dilution of 1:400 is the presence of GM3 ganglioside detected. The presence of anti-GM3 antibodies is noted only at dilutions of 1:40 and 1:400 (Fig. 1J).

In the total brain extract, only at dilution 1:200 there is a higher titer of anti-GM1 antibodies (Fig. 2B) compared to the titer of GM1 ganglioside (Fig. 2A). At all other dilutions (1:40, 1:100, and 1:400), significantly higher titers of GM1 ganglioside are found compared to anti-GM1 antibody titers. At dilutions from 1:100 to 1:400 of the brain sample containing molecules with affinity to GSH, GM1 ganglioside titers (Fig. 2A) were significantly higher than anti-GM1 antibody titers (Fig. 2B). Only at dilution 1:40 of the same sample, approximately equivalent titers of GM1 ganglioside and anti-GM1 antibodies are found. A similar pattern is observed in the pancreas samples. Here, a significantly higher titer of GM1 ganglioside compared to the titer of anti-GM1 antibodies is found only at 1:100 dilution in both total extract (Fig. 2C) and sample containing molecules with affinity to GSH (Fig. 2D). Only at 1:40 dilution of the pancreas sample containing molecules with affinity to GSH is there a significantly higher titer of anti-GM1 antibodies (Fig. 2D) compared to the titer of GM1 ganglioside (Fig. 2C). At all other dilutions of the total extract from the same organ and the sample containing molecules with affinity to GSH, statistically insignificant differences are observed between the titers of GM1 ganglioside and anti-GM1 antibodies (Fig. 2C, Fig. 2D). Only at dilution 1:200 of the total myocardium extract are the titers of GM1 ganglioside and anti-GM1 antibodies approximately equivalent (Fig. 2E). At all other dilutions of the same sample (1:40, 1:100, and 1:400), higher anti-GM1 antibody titers are reported compared to GM1 ganglioside titers, and at 1:100 and 1:400 dilutions, this difference is statistically significant in contrast to the results at 1:40 dilution. Regarding the myocardium extract sample containing molecules with affinity to GSH, at dilutions from 1:40 to 1:200, significantly higher anti-GM1 antibody titers are found than GM1 ganglioside titers at the same dilutions (Fig. 2F). Only at 1:400 dilution of the same sample is the opposite result observed.

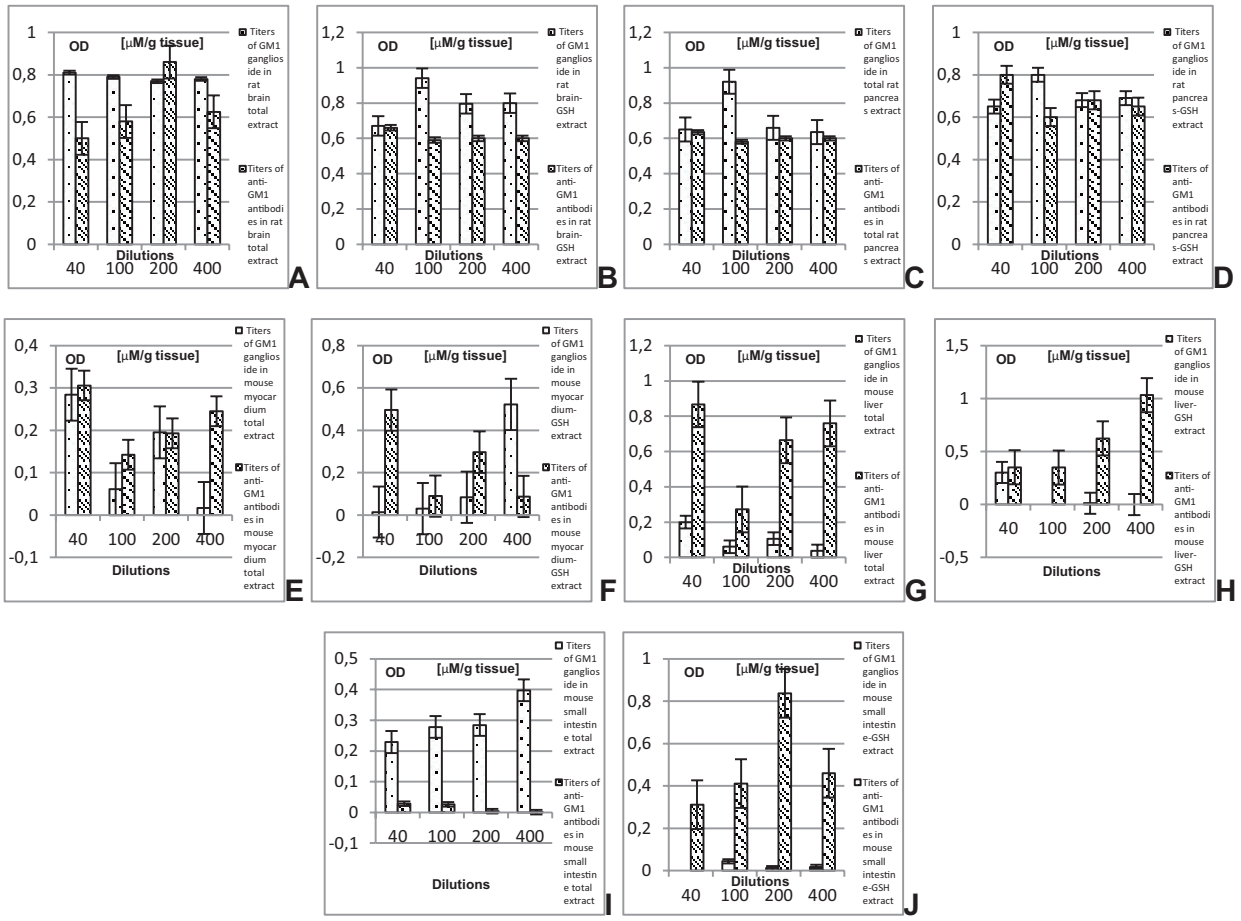

Figure 2. Titers of ganglioside GM1 and anti-GM1 antibodies in extracts from rodent brain (**A, B**), rodent pancreas (**C, D**), rodent myocardium (**E, F**), rodent liver (**G, H**), rodent small intestine (**I, J**); **A, C, E, G, I**—control samples; **B, D, F, H, J**—containing molecules possessing affinity to tripeptide GSH.

In the total liver extract at all dilutions, significantly higher anti-GM1 antibody titers are detected than GM1 ganglioside titers (Fig. 2G). The opposite data are observed in the total small intestine extract (Fig. 2I). In the sample from liver extract containing molecules with affinity to GSH, the presence of anti-GM1 antibodies as well as of GM1 ganglioside is reported only at dilution 1:40, and the difference in titers is not statistically significant (Fig. 2H). In the small intestine extract sample containing molecules with affinity to GSH, at dilutions from 1:100 to 1:400, significantly higher anti-GM1 antibody titers are reported compared to GM1 ganglioside titers (Fig. 2J). The presence of GM1 ganglioside is not detected only at 1:40 dilution of the same sample.

In the total brain extract at 1:40, 1:100, and 1:400 dilutions, higher titers of GD1a ganglioside are observed compared to the anti-GD1a antibody titers, but only at 1:100 dilution is the difference statistically significant (Fig. 3A). At dilution 1:200 of the same sample, approximately equivalent titers of GD1a ganglioside and anti-GD1a antibodies are reported. A similar observation is made in the brain extract sample containing molecules with affinity for GSH, the only difference being the significantly higher titer of the anti-GD1a antibodies at 1:100 dilution (Fig. 3A) compared to the titer of GD1a ganglioside at the same dilution (Fig. 3B). At 1:200 and 1:400 dilutions in the total pancreas extract, there are significantly higher titers of GD1a ganglioside compared to anti-GD1a antibody titers at the same dilutions (Fig. 3C). In the sample containing molecules with affinity for GSH, a significantly higher titer of GD1a ganglioside compared to the titer of anti-GD1a antibodies is detected only at dilution 1:400 (Fig. 3D). Approximately equivalent titers of GD1a ganglioside and anti-GD1a antibodies are reported in the total pancreas extract at 1:40 and 1:100 dilutions (Fig. 3C). In the sample containing molecules with affinity to GSH, only at dilution 1:200 is the titer of anti-GD1a antibodies higher compared to the ganglioside titer (Fig. 3D). An opposite result is reported at 1:40 and 1:100 dilutions of the same sample. At all three dilutions (from 1:40 to 1:200), the differences between the titers of GD1a ganglioside and of anti-GD1a antibodies are not statistically significant. At 1:40 and 1:100 dilutions of the total myocardium extract, no presence of GD1a ganglioside is reported (Fig. 3E) except for the result at 1:40 dilution of the sample of the same organ containing molecules with affinity to GSH (Fig. 3F). At 1:200 dilution of the total myocardium extract, there is a statistically higher titer of GD1a ganglioside compared to the titer of the anti-GD1a antibodies (Fig. 3E).

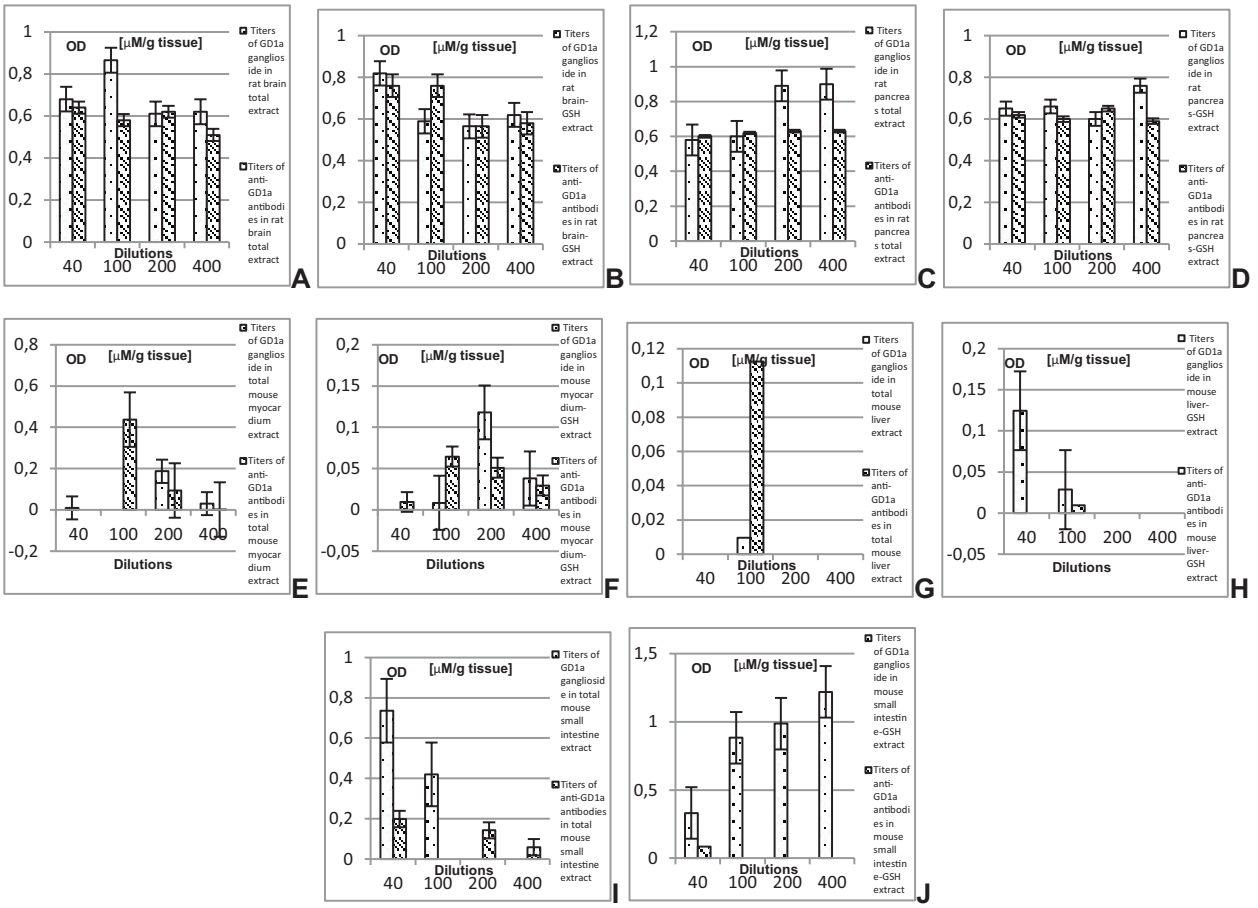

Figure 3. Titers of GD1a ganglioside and anti-GD1a antibodies in extracts from rodent brain (**A, B**), rodent pancreas (**C, D**), rodent myocardium (**E, F**), rodent liver (**G, H**), rodent small intestine (**I, J**); **A, C, E, G, I**—control samples; **B, D, F, H, J**—containing molecules possessing affinity to tripeptide GSH.

A similar result is observed at the same dilution of the myocardium extract sample containing molecules with affinity to GSH (Fig. 3F). At 1:400 dilution of the same sample, a higher titer of GD1a ganglioside is also observed compared to the titer of anti-GD1a antibodies, but the difference is not statistically significant. Only at dilution 1:100 of the total liver extract is established the presence of both GD1a ganglioside and anti-GD1a antibodies, as opposed to the other dilutions, where neither component is detected (Fig. 3G). The titer of the anti-GD1a antibodies is significantly higher compared to the titer of GD1a ganglioside. Similar data are found at 1:100 dilution of the liver sample containing molecules with affinity to GSH, but here, as well as at dilution 1:40, the presence of GD1a ganglioside is reported (Fig. 3H). Only at 1:40 dilution of the total small intestine extract is there a presence of both GD1a ganglioside and anti-GD1a antibodies, with the titer of the ganglioside being significantly higher than the titer of the anti-GD1a antibodies (Fig. 3I). At 1:100 dilution of the same sample, only ganglioside is detected, and at 1:200 and 1:400 dilutions, only anti-GD1a antibodies, respectively. Similarly, only at 1:40 dilution of the small intestine sample containing molecules with affinity to GSH there is a presence of GD1a ganglioside and anti-GD1a antibodies, and here again the ganglioside titer is significantly higher than the titer of antibodies (Fig. 3J). At the remaining dilutions of the same sample (from 1:100 to 1:400), there is a presence of GD1a ganglioside only, but not of anti-GD1a antibodies. The titers of GD1a ganglioside at the three dilutions are higher than the titers of the same ganglioside at the same dilutions of the samples from the other investigated anatomic organs. Similar fluctuations are found in the dilutions of the small intestine samples. In contrast to the data for the myocardium and liver samples, in individual dilutions of each of them compared to the corresponding dilutions of samples from all other investigated small intestine samples, there are abnormally high titers of gangliosides or of specific antibodies.

Discussion

The presented results support the literature data regarding the role of gangliosides as markers of malignancy on the one hand, but also regarding their preventive effect against neoplasms on the other (Kabayama et al. 2007; Sasaki et al. 2015). The current data are also in agreement with literature findings regarding the role of these molecules in the prevention of other pathologies (diabetes, neurodegenerative disorders, etc.) again through their participation in specific intermolecular interactions (Takeda et al. 1989; Putaala et al. 2001). According to a number of literature data, GM1 and GM3 gangliosides each act through different mechanisms by influencing different key intermolecular interactions and regulatory mechanisms (Mutoh et al. 1995; Hashiramoto et al. 2006). The indirect effect of GD1a ganglioside in these interactions has also been demonstrated, which in the present study was confirmed by the observed variations in the titers of this ganglioside and of the antibodies to it (Mukherjee et al. 2008; Rong et al. 2013). The obtained results show significantly lower titers of the three gangliosides and of the specific antibodies to each of them in myocardium and liver samples compared to brain and pancreas samples. At specific dilutions of the myocardium and liver samples, the absence of one or more gangliosides or of specific antibodies against one or more of the tested gangliosides is established. On the other hand, the present pilot study also confirms the key role of GSH in the functions of different cells, tissues, and organs through its participation in different intermolecular interactions depending on the surrounding environment (Zurita et al. 2001). An explanation of these data is related to the higher amounts of *de novo*-synthesized and/or free unbound GSH, as well as free gangliosides, in the myocardium and liver, as proven in the literature, taking into account that the myocardium and liver are known as the organs with the highest content of GSH. In contrast to these two anatomic organs, active intermolecular interactions with the participation of these molecules are found in the brain and pancreas. The established variations in the titers of the three tested gangliosides, as well as of the specific antibodies against each one of them, can also be explained by their property to convert into each other. In agreement with literature data, the established alternation of a complete absence of gangliosides or of anti-ganglioside antibodies in individual dilutions of the small intestine extract samples with unusually high titers compared to the respective dilutions of the samples from the other investigated organs can be explained by the presence of the intestinal microflora (Wu et al. 1995; Chen et al. 2009; Patry et al. 2019; Brown et al. 2023). The absence of a ganglioside or of a corresponding anti-ganglioside antibody can also be explained by the influence of bacterial neuraminidases/sialidases (Juge et al. 2016). The obtained results also show the possibility of the production of antibodies/immunoglobulins by non-lymphoid cells, tissues, and organs, including by malignant cells and neoplastic formations, in specific conditions (Otey et al. 2009; Kappler and Hennet 2020). One of the explanations is associated with the performance of other functions (such as functions as enzymes, neurofilaments, etc.) by these proteins or by individual domains/chains of the immunoglobulin molecule when such cells do not exhibit immune properties (Grant et al. 1992; Willis et al. 2013). According to another hypothesis, in the presence of neoplastic cells or malignant antibodies, microorganisms or microbial antibodies, cytokines, immunomodulators, etc., individual subgroups of cells from the investigated organs differentiate in a lymphoid direction in the early stages of their maturation.

Conclusions

A number of proteins perform besides the role of tumor suppressors also the role of neuroprotectors, endocrine regulators, and antidiabetic substances. In this regard, the

present study determines the titers of GM3, GM1, and GD1a gangliosides, as well as of specific IgG antibodies to each of them, in rodent brain, pancreas, myocardium, liver, and small intestine. A total extract (control sample) containing the complete set of molecules is prepared from each organ. An equivalent amount of the extract is passed through a GSH-agarose column in order to select the molecules from each organ possessing affinity to the reduced form of glutathione tripeptide (GSH). Enzyme-linked immunosorbent assay (ELISA) is used to determine the titers of the above-mentioned gangliosides and the antibodies against each of them. According to the obtained results, significantly lower amounts of the three tested gangliosides and of the specific antibodies against them are reported in the myocardium and liver samples, compared to the brain and pancreas samples. Taking into account that the myocardium and liver are the organs known to have the highest content of GSH, the observed results can be explained by high concentrations of free and/or newly synthesized GSH in them, which does not participate in intermolecular interactions, unlike GSH in the other investigated organs. Deviations found in the small intestine samples varying from a complete absence of any of the three tested gangliosides or of specific anti-ganglioside antibodies at certain dilutions to the highest titer of ganglioside or of specific antibodies compared to the rest of the organs at other dilutions can be explained by the presence of the intestinal microbiome, including the influence of bacterial neuraminidases/sialidases. The presented data prove the possibility of the production of antibodies by non-lymphoid cells, tissues, and organs in specific conditions. Since the antibodies thus produced are outside the germinal centers of specialized lymphoid tissues and organs, regulation of their production and functions by specific interactions with small ions and/or molecules such as gangliosides is of significant importance. In the conducted study, the attention is focused specifically on intermolecular interactions involving the three tested gangliosides and the GSH tripeptide. The main idea is aimed at researching the mechanisms underlying the interaction between the separate organs and systems in the body.

Conflicts of interest

The authors declare no conflicts of interest.

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