Chapter 2

Brain Gangliosides and Their Function as Natural Adaptogenes

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Abstract

In brain gangliosides and phospholipids of stenothermal cold-water teleost fishes, higher content of polyenoic and monoenoic fatty acids was revealed than in brain gangliosides and phospholipids of warm-water stenothermal teleosts. The changes in fatty acid composition of lipids during adaptation of fishes to living in cold water (or at great water depth) are directed to the maintenance of liquid-crystalline state of cell membranes and their optimal fluidity, physical state, and microheterogeneity. The results of cluster analysis of the data on composition of carbohydrate component of brain gangliosides of various ectothermic vertebrates were used to create the dendrogram. This dendrogram was found to correspond appreciably to the tree of classical taxonomy of vertebrates. The changes in molecular organization of brain gangliosides in the course of evolution of vertebrates are suggested to contribute to differentiation of brain and complication of its functions in phylogenesis. The main brain gangliosides (GM1, GD1a, GD1b, GT1b) may be considered to be typical adaptogens. They protect neurons against the action of excitatory amino acids, hydrogen peroxide, amyloid β-peptide, and other toxins. Protective effect of gangliosides against these toxins depends on activation of Trk receptor tyrosine kinase and downstream protein kinases.

Keywords: gangliosides, adaptogens, neuroprotection, signal transduction pathways

1. Introduction

From the beginning of 1960s of the previous century till the present time, the main investigations in the laboratory of comparative neurochemistry of our Institute (from 2014 becoming a part of laboratory of molecular endocrinology and neurochemistry) were devoted to studies of brain lipids. This choice was made by Professor E.M. Kreps, who founded the laboratory

and was its head for many years. Professor Kreps was a prominent and outstanding scientist. He was a member of Russian Academy of Science (RAS) and for many years, a Head of Division of Physiology of Russian Academy of Sciences. Professor E.M. Kreps had a gift of scientific foresight, as in 1960s, studies of cell membrane lipids did not attract much attention from investigators. But later it became evident that such studies were necessary for understanding of biochemical mechanisms of action of hormones, second messengers, mediators, and other physiologically active compounds, of processes of animal adaptation to changes of environment and functional activities, and of mechanisms of various disease pathogenesis. The clinical trials of various lipids may result in appearance of new drugs. In the laboratory of comparative neurochemistry, the comparative studies of various lipids, including phospholipids, cholesterol and its esters, cerebrosides, sulphatides, and gangliosides, were performed [1–3]. The aim of the present short review is to describe as an example of comparative brain lipid investigations performed under the guidance of Professor E.M. Kreps the studies of vertebrate brain gangliosides and to characterize the recent data on the mechanism of exogenous ganglioside protective action on neurons and cells of neuronal cell lines obtained by his collaborators.

2. Changes in brain ganglioside fatty acid composition as a result of natural adaptations of fishes to the conditions of environment

Gangliosides are the most complex glycolipids in animals, containing sialic acids. The four main brain gangliosides in mammals (GM1, GD1a, GD1b *и* GT1b) consist of fatty acid, long-chain base residues and carbohydrate chain of four monosaccharides which form bonds with 1–3 sialic acid residues. Gangliosides appeared at relatively late stages of animal evolution, as components of cell membranes of various organs of Deuterostomia (types of Echinodermata and Chordata). It was shown that in the course of evolution of vertebrates, ganglioside content of brain increases along with the increase in the degree of brain differentiation leading to its more complex organization [3, 4]. Comparative study of cell membrane lipids of various organs appears to be a fruitful approach to elucidation of their role in adaptation of organisms to changing conditions of environment and functional activity [3, 5].

The differences in fatty acid composition of brain gangliosides were found to be highly significant when stenothermal teleosts living at low and relatively high water temperature were compared. These differences are more pronounced than the differences in fatty acid composition of phospholipids (**Figure 1**). Probably, it may be due to the fact that the main places of ganglioside localization in vertebrates are plasma membranes of neurons, including their synaptic membranes, the maintenance of their functional activity at optimal level being especially important to organisms [5]. Thus, saturated fatty acids content in brain ganglioside was much lower in cold-water stenothermal teleosts than in warm-water ones (83.4 ± 1.5 and 50.9 ± 4.9% from total fatty acid content, respectively). The content of monoenoic and polyenoic fatty acids in brain gangliosides was, on the contrary, much higher (**Figure 1**) in cold-water fishes (35.3 ± 3.6% and

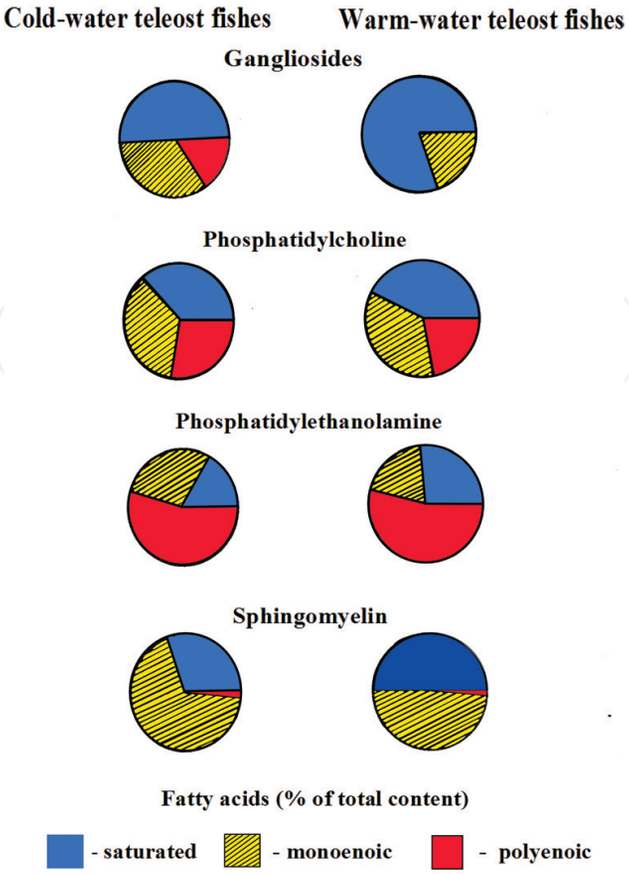

Figure 1. Fatty acid composition of lipids from brain of warm-water and cold-water stenothermal species of teleost fishes.

13.8 ± 4.0%, respectively), as compared with warm-water fishes (16.1 ± 1.6% and less than 1% from their total content, respectively). The differences between the two groups of fishes were highly significant ($p < 0.01$ in all cases).

Fatty acid composition of gangliosides and phospholipids from brain of seven stenothermal cold-water teleost species living at water temperature of 0–10°C (*Bathylagus antarcticus*, *Lampanyctus australis*, *Antimora rostrata*, *Coelorinchus* sp., *Comephorus baicalensis*, *Comephorus dybowskii*, *Cottocomephorus inermis*) and of seven stenothermal warm-water teleost species living at temperature of 23–25°C (*Cheilopogon exsilience*, *Lepophidium profundorum*, *Calamus* sp., *Coryphaena hippurus*, *Lethrinus chrysostomus*, *Rhomboplites aurorubens*, *Sphyraena picudilla*) is shown in **Figure 1**. The highest content of unsaturated fatty acids in brain gangliosides was characteristic of the fishes living in water at great depth. At adaptations of fishes to environmental temperature, the most pronounced changes was revealed in the contents of fatty acids 18:0, 22:1, 24:1, and 22:6 ω3 in brain phospholipids and gangliosides, and they may be called "the adaptation tools" [3].

At the natural adaptations of cartilaginous and ganoid fishes to the temperature of the habitat, the changes in the content of saturated and monoenoic fatty acids in brain gangliosides were

revealed, while polyenoic fatty acids were practically absent in these brain lipids. Studying 37 species of cartilaginous, ganoid, and teleost fishes it was found [6] that the portion of saturated fatty acids in brain gangliosides increased essentially and significantly at augmentation of the environmental temperature ($r^2 = 0.21$, $r = 0.46$, $p < 0.005$). In contrast, the contents of monoenoic and long-chain fatty acids in fish brain gangliosides correlated negatively to the environmental temperature ($r^2 = 0.26$, $r = -0.51$, $p < 0.002$ and $r^2 = 0.34$, $r = -0.58$, $p < 0.001$, accordingly), but the correlation between the content of polyenoic fatty acids in brain gangliosides of teleost, ganoid, and cartilaginous fishes and the temperature of their habitat was not revealed [6]. It may be explained by the fact that polyenoic fatty acids are characteristic mainly for gangliosides from teleost brain but not for gangliosides from ganoid and cartilaginous fish brain [3, 7].

The introduction of one double bond in the fatty acid molecule decreases the temperature of its melting point by several tens of degrees, and the introduction of several double bonds in the molecule has more pronounced effect. The differences in brain ganglioside fatty acid composition of warm-water and cold-water species appear to be the results of idioadaptations of fishes to the temperature of their habitat. They are directed to the maintenance of brain cell membrane fluidity, physical state, and microheterogeneity at the optimal level for function of enzymes, receptors, and other bioactive compounds and make possible the survival of animals in changing conditions of environment.

3. The differences in the structure and composition of carbohydrate component of ganglioside molecule between representatives of various vertebrate classes

We did not reveal the correlation between the composition and structure of brain ganglioside carbohydrate component and the water temperature at which the fishes are living. It was of interest to apply one of the cluster methods of analysis which may provide objective interpretation of a large amount of experimental data [6]. To estimate the similarity or the difference of various species, a number of features of their organization may be used which may be determined quantitatively. We have not met in the literature such studies devoted to brain lipids. In our case, the construction of dendrograms was carried out by the unweighted pair-group method of averages. “Unweighted” means that each of the parameters has equal significance or “weight”.

The content of individual gangliosides (GP, GQ, GT1b, GD1b, GD1a, GD3, GM1) and the summarized content of their two minor fractions (GM2 + GM3) in brains of 24 species of exothermic vertebrates, investigated by us, were used as the eight parameters of the molecular organization, capable of being evaluated quantitatively. (To characterize ganglioside structure we used the nomenclature of Svennerholm, which is the most widely used nomenclature of gangliosides. Letters M, D, T, Q, and P indicate the number of sialic acid residues in the ganglioside molecule mono, di, tri, tetra, and pentasialogangliosides, respectively. Thus, GM1 is monosialoganglioside. The figure (1) corresponds to four saccharide residues, (2) corresponds

to three saccharide residues, and (3) corresponds to two saccharide residues in the ganglioside molecule. These parameters were evaluated as percentage of the total content of brain gangliosides of the species and were expressed in arbitrary units. The content of the ganglioside was expressed as value 1 if its content in the brain of this species is equal to 1–10%, as value 2 at 11–20%, as value 3 at 21–40%, as value 4 if the content was more than 40%. If the content of ganglioside fractions in the brain of a species was less than 0.5% of total brain gangliosides, it was labeled by the 0 value. Then, the dendrograms were generated by PAUP program ver.4.0b8 for Mackintosh using the unweighted pair-group method of averages optimized according to the maximum parsimony principle [6].

The dendrogram, constructed based on the cluster analysis of the data on composition of carbohydrate component of brain gangliosides of the ectothermic vertebrates (**Figure 2**), corresponds appreciably to the tree of classical taxonomy of vertebrates. The species of cartilaginous and ganoid fishes form separate clusters and are sisterly branches for each other. Species of these fishes do not form sisterly groups with any representatives of teleosts, amphibians, or reptilians. All teleost fishes are in ranges of single separate branches on the cladogram. But in contrast to the classical systematics of the vertebrates, two investigated species of amphibians (of Anura group) do not form a separate branch but stand among species of teleosts forming sisterly groups with their species. Probably, these animals have the composition of brain ganglioside carbohydrate component characteristic of their common ancestors. It should also be noted that there is a great difference in the level of central nervous system organization between various species of teleost fishes. It is well known to the zoologist that some species of teleosts have a more differentiated and higher organized brain than representatives of the class of Amphibia. If the level of brain organization has an influence on the structure and

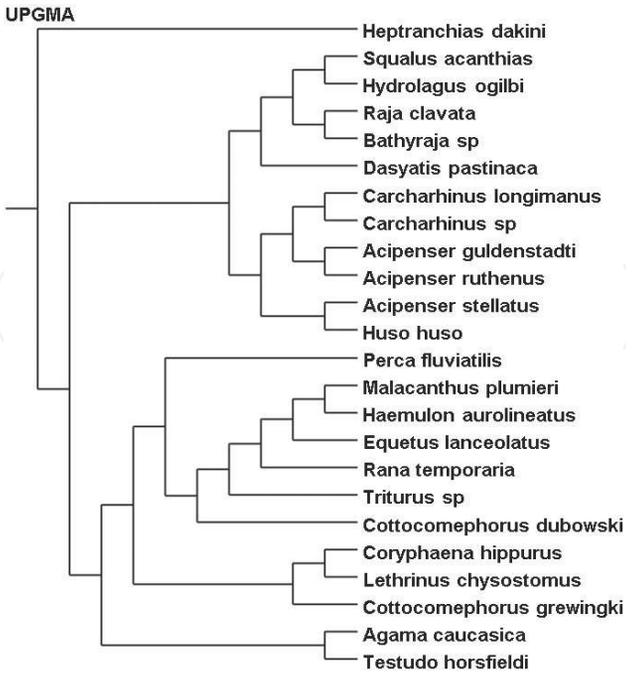

Figure 2. The dendrogram of relative similarity of different vertebrate species according to the parameters of the molecular organization of the carbohydrate component of the brain gangliosides.

composition of brain ganglioside carbohydrate component, it may explain why Anura do not form a separate branch on the dendrogram. In contrast to amphibians, the investigated reptilians form a separate branch on the dendrogram (**Figure 2**).

Among the higher vertebrates, only reptilians are submitted on the cladogram. But much lower content of polysialogangliosides and much higher portion of monosialogangliosides are characteristic of both reptilian and avian and mammalian brain in comparison with the lower vertebrate brain. As it is known, there were cardinal modifications in the organization of animals and their separate organs at entrance of vertebrates on dry land, which are a typical example of an aromorphosis [8]. Carbohydrate components of the glycolipids and glycoproteins play an essential role in cell differentiation and intercellular interaction, including cell recognition and adhesion, especially in the development of organs and tissues. Modifications of the brain gangliosides composition and structure, associated with appearance of the higher vertebrates, have provided, apparently, together with many other biochemical modifications, the molecular bases of the aromorphosis at transferring of vertebrates to the terrestrial lifestyle and amniotic development of embryos, that was accompanied by differentiation and complication of brain functions.

Other differences in composition of the brain gangliosides in various vertebrate classes are observed in the comparison of bony and cartilaginous fishes. They, in particular, reflect elongation of the carbohydrate chain of these lipids during evolution of vertebrates; it is typical also of ontogenetic development of mammals. These modifications of brain gangliosides composition in vertebrates may be also suggested to be associated with aromorphic modifications in the organization of animals.

In our research, the ganoid fishes have formed a single cluster; simultaneously, they are included into sisterly group with high-organized cartilaginous fishes. Views of zoologists on systematic position of the ganoid fishes are inconsistent. These fishes are surveyed as one of the superorders of the class of bony fishes. But some zoologists, on the contrary, emphasize a common origin of ganoids and cartilaginous fishes (e.g., see [9]. Our results (**Figure 2**) correspond with the data of the latter group of morphologists. Researches of hybridization of DNA of various fish species [10] and the study of composition and structure of various lipids (phospholipids, gangliosides, cerebrosides, and sulphatides) from fish brain [3] provide evidence that ganoid fishes have essential difference both from teleosts and from cartilaginous fishes that it is necessary to consider them as the taxon of the higher order than one of the superorders of bony fishes, probably, as a separate class or subclass.

4. Protective effect of main brain gangliosides (GM1, GD1a, GD1b, and GT1b) on damaged nerve cells or cells of neuronal cell lines

Gangliosides possess the functions of adaptogenes not only in ectothermic animals but in mammals too. It appears not to be due to the changes of brain ganglioside fatty acid composition, as the relative content of their saturated and unsaturated fatty acids was shown not to change as a result of cold stress [11]. But exogenous gangliosides administered to mammals with damaged brain increase the viability of brain neurons and improve the functional state

of the animals, if the injury is caused by ischemia and reperfusion, various toxins, or trauma. Brain gangliosides possess the protective action on cultured neurons as well. The protective effect is characteristic for the main brain gangliosides (GM1, GD1a, GD1b, and GT1b). The most stable ganglioside GM1 is usually used in such experiments. It was found that the protective effect of GM1 against the toxic action on the nerve cells of serum-free medium devoid of growth factors or glutamate depended on the activation of Trk receptor tyrosine kinase [12–14]. We have for the first time shown that GM1 ganglioside increases the viability of nerve cells or cells of neuronal lines at application of other toxic compounds—of amyloid peptides [15–17] or hydrogen peroxide [14], the protective action of GM1 being also based on the activation of Trk receptor tyrosine kinase.

5. Gangliosides exert the protective effect on neurons and cells of neuronal cell lines not only at micromolar concentrations but at nanomolar concentrations as well

The protective effect of gangliosides on cultured nerve cells is, as a rule, studied using their micromolar concentrations (10–50 μM). But in cerebrospinal fluid (CSF) and in brain intercellular space of humans and animals, gangliosides are present in nanomolar concentrations. Thus, the total content of four main brain gangliosides (GM1, GD1a, GD1b, and GT1b) was found to constitute on average 92 nM in human CSF [18]. The physiological concentrations of gangliosides which act on brain nerve cells from outside in vivo appear to be nanomolar concentrations. We were the first to show that the protective effect of gangliosides against the toxic action of glutamate on cerebellar granule cells is well expressed both in micro and at nanomolar concentrations [19]. Thus, glutamate increased the number of dead granule cells from 12 ± 3% to 47 ± 4% of total cell number. But if granule cells were preincubated with 10 nM or 10 μM GM1 prior to application of glutamate, then the number of dead neurons decreased to 24 ± 4% and to 20 ± 5%, respectively ($p < 0.01$ in all cases). Gangliosides GD1a, GD1b, and GT1b at nanomolar concentrations also increased granule cells' viability. Later on [14], it was shown by us that the protective effect of GM1 at nanomolar concentrations also depended on activation of Trk receptor tyrosine kinase, as it was previously shown for gangliosides at micromolar concentration.

GM1 and GD1a gangliosides at nanomolar concentrations increase the viability of the cells of neuronal line PC12 exposed to hydrogen peroxide as well, their effect being also mediated by activation of Trk receptor tyrosine kinase. But in these cells, the protective effect of gangliosides at nanomolar concentrations was lower than their effect at micromolar concentrations [20].

6. The mechanism of neuroprotective effect of GM1 and other main brain gangliosides

Activation by GM1 ganglioside of protein kinase regulated by extracellular signals (ERK1/2) and of protein kinase B (Akt) takes place downstream of Trk receptor tyrosine kinase; it was

shown using brain slices [21] and PC12 cells [20]. Activation of these protein kinases by GM1 is of importance for realization of the protective effect of GM1. Thus, it was shown [20] that the protective effect of GM1 against the toxic action of hydrogen peroxide is significantly diminished in the presence of the inhibitor of ERK1/2, or Akt, or protein kinase C. These data are in agreement with the data showing that ERK1/2 activation by GM1 increases the viability of retinal neurons after the axotomy of optic nerve [22]. But only in the presence of the inhibitors of all these protein kinases, the diminution of the protective effect of GM1 is pronounced and comparable with the effect of the inhibitor of Trk receptor tyrosine kinase which abolishes the protection.

Using immunoblotting it was shown that GM1 ganglioside both at nano and micromolar concentrations activated protein kinase B (Akt) in control PC12 cells [20]. The effect of GM1 on ERK1/2 activity was shown to be more pronounced in micro than in nanomolar concentration. Hydrogen peroxide itself activated ERK1/2. And preincubation of PC12 cells with GM1 at nanomolar concentration and even more at micromolar concentration caused the further increase of ERK1/2 activity in PC12 cells that was significant. The activation of Akt and ERK1/2 was shown to take place downstream of Trk receptor tyrosine kinase [20].

7. GM1 ganglioside normalizes the rate of respiration of PC12 cells and of mitochondria isolated from rat brain, which decreased as a result of prooxidant action

It was shown by us [23] that preincubation of PC12 cells with GM1 ganglioside prevents to a large extent the decrease of the rate of basal and uncoupled respiration, caused by the action of hydrogen peroxide. Besides, GM1 and GD1a gangliosides were shown to normalize the respiratory rates of mitochondria isolated from rat brain and exposed to prooxidant—tret-butyl hydroperoxide (tBHP). GM1 was shown to decrease the ratio of proapoptotic to antiapoptotic proteins Bax/Bcl-xL in control PC12 cells (from 1.0 to 0.79 ± 0.08, $p < 0.05$). As activation of ERK1/2 and Akt may lead to inactivation of proapoptotic protein Bad, which reacts with antiapoptotic proteins like Bcl-2 and Bcl-xL [24], the protective effect of GM1 and its ability to stabilize mitochondria may be a result of activation of these protein kinases [20].

GM1 and GD1a gangliosides were found to normalize the respiration rate of isolated rat brain mitochondria diminished as a result of their exposure to tBHP. It is of interest that the protective effect of these gangliosides was abolished in the presence of the inhibitor of Trk receptor tyrosine kinase K252a. In brain mitochondria, various protein kinases are present, including Trk receptor tyrosine kinase A and B [25, 26]. It was shown [26] that the protective effect of nerve growth factor on isolated brain mitochondria is abolished in the presence of the inhibitor of this protein kinase—K252a. It may be suggested that the protective effect of GM1 and other gangliosides may be to a certain extent due to their action on mitochondrial signaling pathways.

8. GM1 and GD1a gangliosides prevent TLR4 translocation into lipid rafts and protect PC12 cells from the toxic bacterial lipopolysaccharide action

Interesting data were obtained by us together with the group led by Dr. R.G. Parnova from our Institute studying the mechanism of protective effect of gangliosides against the toxic action of bacterial liposaccharide (LPS) which is the main bacterial toxin, initiating meningoencephalites in humans. GM1 and GD1a gangliosides were shown to cause the pronounced increase of viability of PC12 exposed to toxic concentrations of LPS. Their protective effect against LPS action on PC12 cells was found not to depend on modulation of Trk receptor tyrosine kinase, and it was not revealed if PC12 cells were exposed to GM1 and GD1a in nanomolar concentration [27]. The protective effect of these gangliosides was similar to the protective effect of methyl-beta-cyclodextrin, which is known to destroy lipid rafts in cell membranes. It is known that LPS recognition and receptor complex formation occur in lipid rafts, and gangliosides play a key role in their formation and maintenance. Using subcellular fractionation, in combination with immunoblotting, and antibodies to TLR4 and flotilin (a marker of lipid rafts), it was shown that pretreatment of PC12 cells with GM1 ganglioside completely eliminated the effect of LPS on translocation of TLR4 into lipid rafts that is necessary to induce the toxic effect of LPS on the cells.

Most probably it can be explained by the fact that ganglioside incorporation in cell plasma membranes changes raft composition and properties. The results obtained suggest that ganglioside-induced prevention of TLR4 translocation into lipid rafts is a mechanism of protection against LPS action in various cells. Thus, the mechanism of protection by gangliosides against the toxic action of LPS appears to be quite different from the mechanism of their protection against the toxic effect of long incubation in serum-free medium and against glutamate, amyloid beta-peptide, or hydrogen peroxide action on the nerve cells which is mediated by activation of Trk receptor tyrosine kinase.

9. Conclusion

The considerable differences in brain lipid fatty acid composition were revealed between stenothermal cold-water and warm-water teleost fishes. The differences in fatty acid composition of brain gangliosides (which are characteristic components of neuronal plasma membranes including synaptic membranes) were found to be more pronounced between these two groups of teleosts than the differences in brain phospholipid fatty acid composition. The increase of relative content of monoenoic and polyenoic fatty acids (especially of 22:1, 24:1, and 22:6 ω3) in the brain lipids of teleost species living in cold water appears to be an important part of natural adaptations of these fishes to the conditions of their environment. Such changes in composition during adaptation to living in cold water (or at great water depth) provide the preservation of liquid-crystalline state of cell membranes and the maintenance of

optimal cell membrane fluidity and microheterogeneity for the function of enzymes, receptors, and other proteins. In cartilaginous and ganoid fishes, the adaptation to living in cold water appears to be reached mainly by the increase of monoenoic fatty acid content in brain gangliosides, as polyenoic fatty acids were revealed (in low content) only in brain gangliosides of the few species of these fishes.

The correlation between the composition and structure of brain ganglioside carbohydrate component and the water temperature at which the fishes are living was not revealed. The dendrogram, constructed based on results of the cluster analysis of the data on composition of carbohydrate component of brain gangliosides of the ectothermic vertebrates, corresponds appreciably to the tree of classical taxonomy of vertebrates. The species of cartilaginous and ganoid fishes form separate clusters and are sisterly branches for each other. Species of these fishes do not form sisterly groups with any representatives of teleosts, amphibians, or reptilians. All teleost fishes are in ranges of the single separate branch on the dendrogram. The studied reptilians form a separate branch on the dendrogram.

Among the higher vertebrates, only reptilians are submitted on the cladogram. But much lower content of polysialogangliosides and much higher content of monosialogangliosides as compared to lower vertebrate brain are characteristic not only for reptilian brain but for avian and mammalian brain as well. As is known, there were cardinal modifications in the organization of animals and their separate organs at entrance of vertebrates on dry land, which are a typical example of an aromorphosis [8]. Carbohydrate components of glycolipids and glycoproteins play an essential role in cell differentiation and intercellular interaction, including cell recognition and adhesion, especially in development of organs and tissues. Modifications of the brain gangliosides composition and structure, associated with appearance of the higher vertebrates, may be suggested to provide, apparently, together with many other biochemical modifications, the molecular bases of the aromorphosis at transferring of vertebrates to the terrestrial lifestyle and amniotic development of embryos that was accompanied by differentiation and complication of brain functions.

The administration of exogenous GM1 or other main brain gangliosides (GD1a, GD1b, GT1b) to animals with the damaged brain protects brain neurons from death and improves the functional state of the animals. Various main brain gangliosides have the similar effects as typical adaptogens. The increase by GM1 of the viability of neurons and of cells of neuronal lines treated by glutamate or left in media devoid of neurotrophic factors was shown to depend on activation of Trk receptor tyrosine kinase. According to our data, GM1 ganglioside also protects neurons and PC12 cells against toxic action of amyloid peptides and hydrogen peroxide. This effect is also mediated by Trk receptor tyrosine kinase. It was shown that GM1 and other main brain gangliosides exert the protective effect on nerve cells not only at micromolar concentration but at nanomolar concentration as well, which appears to be their physiological concentration in cerebrospinal fluid and intercellular brain space. GM1 ganglioside normalizes the rate of respiration of PC12 cells and of mitochondria isolated from rat brain, decreases the proapoptotic to antiapoptotic protein ratio Bax/Bcl-xL, and activates ERK1/2 and Akt downstream of Trk receptor tyrosine kinase. Another mechanism of protective effect of GM1 and GD1a gangliosides was revealed studying their ability to increase the viability

of PC12 cells exposed to bacterial LPS. In this case, the protection was not mediated by Trk receptor tyrosine kinase. The results obtained suggest that ganglioside-induced prevention of TLR4 translocation into lipid rafts is a mechanism of protection of cells against the effect of LPS, as LPS interaction with its receptor in lipid rafts is necessary to induce its toxicity. The understanding of the mechanism of the protective effect of gangliosides on nerve cells is of importance for the increase of the efficiency of clinical trials of these lipids as drugs for the treatment of ischemic, neurodegenerative, and other diseases concerned with central nervous system damage.

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