

Recognition-behavioral stress-coping humoral glycolipids produced by medicated major psychoses patients

Yutaka Masuda (✉ y-masuda@hos.akita-u.ac.jp)

Research article

Keywords: Mammalian recognition-behavioral stress-coping system; Humoral glycolipids; Major psychoses patients; Emotional and recognition-behavioral symptoms; Medication; Biomarker identifying schizophrenia

Posted Date: September 17th, 2019

DOI: <https://doi.org/10.21203/rs.2.14531/v1>

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Abstract

Background Mammalians have the recognition-behavioral stress-coping system regulated via the neuronal modules followed by some humoral glycolipids. A sulfated Galbeta1-4GlcNAc-lipid promotes the serotonergic module. GalNAcalpha1-3GalNAc-lipid promotes the adrenergic module. A Fucalalpha1-2Glc-lipid protects the cholinergic module. Sialalpha2-3Gal-lipid promotes the dopaminergic module.

Methods Major psychoses patients show the emotional and recognition-behavioral symptoms, and long-time medication does not completely delete the symptoms. I examined the recognition-behavioral stress-coping humoral glycolipids produced by medicated major psychoses patients.

Results The major depression patients produced the sulfated Galbeta1-4GlcNAc-lipid and the sulfated Fucalalpha1-2Glc-lipid, but deduced the GalNAcalpha1-3GalNAc-lipid. The mania patients produced the sulfated Galbeta1-4GlcNAc-lipid. The schizophrenia patients produced the sulfated Galbeta1-4GlcNAc-lipid, and remarkably produced the Sialalpha2-3Gal-lipid. Ruled out the medication-effects, the major depression patients decreased the serotonergic module function and the adrenergic module function, but increased the cholinergic module function. The mania patients increased the serotonergic module function and the adrenergic module function. The schizophrenia patients increased the serotonergic module function, and particularly increased the dopaminergic module function.

Conclusion These suggest the stress-coping humoral glycolipids produced by the patients corresponded to the symptoms. Furthermore, I understood the humoral Sialalpha2-3Gal-lipid would be considered as another biomarker identifying schizophrenia.

Background

Major psychoses patients show the emotional and recognition-behavioral symptoms. Medication decreases the symptoms, but even the long-time medication does not completely delete the symptoms.

In mammalian brains, the amygdala has an important role for inducing the emotional behaviors. The ventral striatum has an important role for determining the behaviors. The caudal nucleus has an important role for learning, and the hippocampus has an important role for memorizing stressors. These brain portions are networked via serotonergic neurons radiated from the raphe nucleus and dopaminergic neurons radiated from the substantia nigra. The cerebral cortex adequately integrates information sent from these brain portions. The networked-portions work as individual neuronal modules [1, 2]. The modules are followed by some humoral glycolipids. A sulfated Galbeta1-4GlcNAc-lipid (3-O-Sulfo-Beta-D-Galactosyl-(1->4)-N-Acetyl-Beta-D-Glucosamine-lipid: sG1-4GN) promotes the serotonergic module regulating the emotional behaviors for not-wasting the physical strength [3, 4], GalNAcalpha1-3GalNAc-lipid (GalNAcalpha1->3GalNAc-lipid: GN1-3GN) promotes the adrenergic module inducing the stress-coping behaviors [5, 6], sulfated Fucalalpha1-2Glc-lipid (Fucalalpha1-2[6OSO3]Galbeta1-4Glc-beta-lipid: sF1-2G) protects the cholinergic module keeping the valid stress-coping memories from the ischemia-stress, as an adaptogen does [4, 7, 8], and Sialalpha2-3Gal-lipid (NeuAcalpha2-3Gal-lipid: S2-3G)

promotes the dopaminergic module integrating the emotion and recognition-behaviors [9, 10, 11]. Now, major depression patients have the functional abnormalities in their amygdala, caudate nucleus and hippocampus [12], manic patients have the functional abnormalities in their amygdala, ventral striatum and hippocampus [13], and schizophrenia patients have the functional abnormalities in their frontal and temporal lobes [14].

The recognition-behavioral stress-coping system of major psychoses patients would abnormally work. Especially, schizophrenia patients alter the glycolipid production in the brain [15, 16], and their neuronal modules are abnormally networked [17, 18]. I hypothesized the major psychoses patients would abnormally produce the recognition-behavioral stress-coping glycolipids even in the medicated state. In the present study, I examine the recognition-behavioral stress-coping glycolipids produced by medicated major psychoses patients, and healthy volunteers as Positive Control.

Methods

Subjects and the sera collection

According to ICD–10, 3 psychiatrists identified major depression patients without psychotic symptoms (DP; 4 women and 2 men, aged from 48 to 62, average 53 years-old), manic patients without psychotic symptoms (MA; 2 women and 4 men, aged from 45 to 62, average 46 years-old) and schizophrenia patients (SZ; 3 women and 3 men, aged from 33 to 59, average 43 years-old) from the inpatients and the outpatients of Department of Neuropsychiatry, Akita University Hospital. They were medicated with antidepressants, lithium carbonate, or atypical antipsychotics for 4–12 weeks. They did not suffer from physical diseases at the identification. These patients and healthy volunteers not-suffering from the psychoses (Positive Control; 3 women and 3 men, aged from 28 to 62, average 38 years-old) agreed to participate in the present study, under the intensive informed consent with preservation of their anonymity and guarantee of the withdrawal agreement. A 2 ml of venous blood was individually collected from their arm vein by a medical doctor, under watching of the other medical doctors. The sera were pooled and restored at 4 °C. All of these procedures were conditioned in accordance with Clinical Study Ethics Committee, Graduate School of Medicine, Akita University (the approval number: 2042).

Humoral lipid fractionation

Humoral lipid fractionation was performed as previously described [4]. Briefly, 1.25 ml of chloroform and 2.5 ml of methanol were added to each 1 ml of the pooled serum. The solution was intensively mixed for 3 min and incubated for 10 min at room temperature (RT). Then, 1.25 ml of chloroform was added to the solution, and followed by intensive mixing for 30 s. A 1 ml of water was added to the solution, and followed by intensive mixing for another 30 s. The mixture was then centrifuged at 150 gravities for 10 min at RT. The lower chloroform layer was collected, and the solvent chloroform was evaporated at RT. The extracted lipids were then suspended in 1 ml of water. The solution was applied to 0.5 ml of an ion

exchanger DE-52 (Whatman Co., Maidstone, UK) column, which had been saturated with 10 mM NaHCO_3 , pH8.3, and washed with water. Samples were eluted with 0.5 ml consecutive washes of 50, 100, 150, 200, 250, and 300 mM NaCl. Fractions eluted with 50, 100, 150, and 250 mM NaCl were then diluted to 1 ml with water as the present samples.

Sulfate-radical elimination

Stress-coping humoral glycolipids fractionated with 100 and 250 mM NaCl are sulfated. Sulfate-radical was eliminated from the glycolipids for measuring the terminal sugar-chain reactivity as previously described [4]. Briefly, lipids were extracted again from 800 μl of the sample solutions by using methanol-chloroform method as described above. The extracted lipids were added 400 μl of the reagent containing silyl-agents of TMS-HT kit (Tokyo Chemical Industry Co. Tokyo, Japan), and then, incubated at 90 °C for 3 h. The solutions were added 800 μl water, and intensively mixed for 30 s.

Measurement of the glycolipid production

Bipolar glycolipids attach to plastic plates in 50 % ethanol solution. A modified Enzyme-Linked ImmunoSorbent Assay (ELISA) was performed for measuring the glycolipids production as previously described [4]. Briefly, the sample solution obtained from the fraction eluted with 50 or 150 mM NaCl, the sulfate-radical-eliminated sample solution obtained from the fraction eluted with 100 or 250 mM NaCl, and physiological saline (PS) as Negative Control, were prepared to 50 % ethanol solution. 100 μl of the solution was poured into a well of a 96-well plastic plate (Sumitomo-Bakelite Co., Tokyo, Japan). The ELISA was performed with the use of 300 μl of 5 % bovine serum albumin (Sigma-Aldrich Co., St. Louis, MO, USA) as a blocker, a biotinized-lectin of *Macckia amurensis* recognizing Sialalpha2-3Gal, that of *Recinus communis* recognizing Galbeta1-4GlcNAc, that of *Dolichos biflorus* recognizing GalNAcalpha1-3GalNAc or that of *Aleuria aurentia* recognizing Fucalalpha1-2Glc, peroxidase-conjugated-avidin (Seikagaku Co., Tokyo, Japan), and the coloring kit (Sumitomo Bakelite Co.). Then, the light absorbance was measured at the dual wavelength of 450/655 nm. The ELISA procedure was individually performed on different 5 plates.

Statistical analyses

Mann-Whitney U-test was used for detecting difference from Positive Control. A $p < 0.05$ was considered as a significant difference.

Results

A sG1-4GN production

A sG1–4GN is produced in the fraction eluted with 100 mM NaCl. The production was detected in all of the samples. The production was increased as the same in the samples obtained from the DP, the MA and the SZ (Table 1).

GN1–3GN production

GN1–3GN is produced in the fraction eluted with 150 mM NaCl. The production was detected in all of the samples. The production was decreased in the sample obtained from the DP (Table 2).

A sF1–2G production

A sF1–2G is produced in the fraction eluted with 250 mM NaCl. The production was detected in all of the samples. The production was increased in the sample obtained from the DP (Table 3).

S2–3G production

A S2–3G is produced in the fraction eluted with 50 mM NaCl. The production was detected in all of the samples. The production was markedly increased in the sample obtained from the SZ (Table 4).

Discussion

A sG1–4GN is produced for not-wasting the physical strength, and the deduction would indicate decrease of the physical strength. GN1–3GN is produced for inducing the valid stress-coping behaviors, and the deduction would indicate invalidity of the stress-coping behaviors. A sF1–2G is produced for keeping the stress-coping memories, and the excessive production would indicate searching more valid stress-coping memory. A S2–3G is produced for integrating the emotion and recognition-behaviors, on the contrary, the excessive production would disturb the integration [9, 10, 11]. Now, Positive Control produced sG1–4GN, GN1–3GN, sF1–2G and S2–3G. This indicates healthy human always prepares these glycolipids for their stress-coping. The DP increased the sG1–4GN production and the sF1–2G production but decreased the GN1–3GN production. Antidepressants increases sG1–4GN production and GN1–3GN production [3, 6]. These suggest the DP had the serotonergic module dysfunction, the adrenergic module dysfunction and the cholinergic module hyperactivity without the medication. The DP could not induce the valid stress-coping behavior, and they would decrease the serotonergic module function for not-wasting the physical strength. On the other hand, they would increase the cholinergic module function for searching a valid stress-coping memory. The MA increased the sG1–4GN production. Lithium carbonate decreases GN1–3GN production of hypomanic patients [5]. These suggest the MA had the adrenergic module hyperactivity and the serotonergic module hyperactivity before the medication. The MA could induce the valid stress-coping behavior by successfully working the adrenergic module, and they would increase the serotonergic module function for continuing the effective stress-coping behavior. The SZ increased the

sG1–4GN production, and remarkably increased the S2–3G production. Psychotic symptoms of schizophrenia patients are induced by the dopaminergic and the serotonergic neuronal hyperactivities [19], and the cognitive dysfunction is closely related to the dopaminergic neuronal hyperactivity [20]. Atypical antipsychotics decrease both of the dopaminergic neuronal activity and the serotonergic neuronal activity, however, the long-time medication does not completely delete the psychotic symptoms and the cognitive disturbance. These suggest the SZ had the dopaminergic module hyperactivity and the serotonergic module hyperactivity in spite of the medication. The SZ might be forced to promote the dopaminergic module for integrating the mismatching input sent from the hyperactive serotonergic module and the not-so active adrenergic module.

The presented humoral glycolipids may be cerebrosides [3, 4, 6]. A ganglioside, one of cerebrosides, induces synaptic plasticity of the hippocampus [21]. The presented recognition-behavioral stress-coping glycolipids would promote synaptic plasticity in the corresponding neuronal modules. In fact, both of the repeated electroconvulsive treatment for major depression patients and the lithium carbonate medication for mania patients increase the synaptic plasticity [22, 23]. Now, the stress-coping glycolipids are produced via the gene expressions. Onset of the major psychoses is closely related to the physical and mental stresses, and these strong stresses accelerate secretions of gene-expressing hormones via Hypothalamus-Pituitary Axis. Especially, levels of the gene-expressing cortisol are different in the brain potions of schizophrenia patients [24], and cortisol-medication sometimes induces psychotic symptoms. Cortisol might induce the S2–3G gene expression in schizophrenia patients.

Some researchers have investigated biomarkers of schizophrenia in the view of the proteins, the metabolites and the RNAs in the peripheral blood [25, 26]. Mechanism of S2–3G produced in the peripheral blood is not be clarified in the present time, however, I understand the humoral glycolipid would be considered as another biomarker identifying schizophrenia.

Conclusion

I examined recognition-behavioral stress-coping humoral glycolipids produced by medicated major psychoses patients. The stress-coping humoral glycolipids productions corresponded to the psychoses symptoms, furthermore, I understood Sialalpha2–3Gal-lipid would be considered as another biomarker identifying schizophrenia.

Declaration

Funding

The present study was performed without financial supports.

Competing interest

I declare I do not have any conflicts of interest.

Availability of data

The raw data of the light absorbance indicating the glycolipid production is shown in Supplementary material.

Abbreviations

Not applicable.

Consent to participate

All of the participants of the presented study were adults. They consented to participate in the study under the intensive informed consent with preservation of their anonymity and guarantee of the withdrawal agreement.

Acknowledgement

The patient-identification and the venous blood-collection were performed by Takashi Kanbayashi MD PhD, Kou Tsutsui MD PhD and Yuuki Oomori MD PhD, Department of Neuropsychiatry, Akita University School of Medicine. I deeply thank them for their helps.

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Tables

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