Significance of Humoral Glycolipids Produced by Patients with A Symptomatic Diagnosis of Major Psychoses

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Abstract
Mammals possess a recognition-behavioral stress-coping organization that functions via network of the serotonergic, adrenergic, cholinergic and dopaminergic neuronal systems followed by humoral glycolipids. I hypothesized that the symptoms of major psychoses are manifestations of the changes in the human recognition-behavioral stress-coping organization. I examined the humoral glycolipids produced by patients symptomatically diagnosed with major psychoses under medication. The results indicated the following: production of the serotonergic system-promoting glycolipid and the adrenergic system-promoting glycolipid was decreased while the cholinergic system-protecting glycolipid production was increased in non-medicated patients diagnosed with major depression without psychotic symptoms; production of the serotonergic system-promoting glycolipid and the adrenergic system-promoting glycolipid was increased in non-medicated patients diagnosed with mania without psychotic symptoms; and the serotonergic system-promoting glycolipid production was increased with an inherent increase in the dopaminergic system-promoting glycolipid production in non-medicated patients diagnosed with schizophrenia with psychotic symptoms. These indicated that the humoral glycolipid production was corresponding to the symptoms of major psychoses, which strongly suggested that the humoral glycolipids were considered as biomarker of major psychoses. I concluded that idea of the human recognition-behavioral stress-coping organization followed by humoral glycolipids would give a neuroscientific view-point to major psychoses-diagnosis which has been phenomenologically performed.

Keywords: Bio-marker; Diagnosis, Humoral Glycolipids; Major Psychoses Symptoms; Recognition-Behavioral Stress-Coping Organization

Introduction
The psychoanalysis-founder Sigmund Freud premised his comprehension of human psychology, qualitative-reasoned the premise, and figured the model of human psychology. I understand that psychological phenomena are fully explained via a systemic model qualitative-reasoned and quantitative-reasoned from the physiological premise. Neuroscientific studies have reported that the mammalian brain mainly functions via a network of the adrenergic, serotonergic, cholinergic and dopaminergic neuronal systems [1-3]. I premised the neuronal system-network as systemic model of human recognition-behavioral stress-coping organization. I investigated the role of humoral glycolipids in the neuronal systems to quantitative-reason the systemic model. I have reported that human stress-coping and the recognition-behavior can simply be qualitative-reasoned as aspects of the systemic model [4]. The onset of major psychoses is closely related to stress. I hypothesized that major psychoses symptoms are also manifestation of the change in human recognition-behavioral stress-coping organization. In the present study, I educate the nature of humoral glycolipids in the recognition-behavioral stress-coping organization, and indicate significance of the humoral glycolipids produced by major psychoses patients.

Nature of The Humoral Glycolipids
Promotion of The Adrenergic System by a Glycolipid

The adrenergic system induces stress-coping behaviors (Fig.1). I observed that mice subjected to forced swimming stress exhibited the stress-coping flight behavior by climbing the apparatus wall [5]. I found that this behavior was induced by a humoral glycolipid which wasd isolated from the fraction eluted with mM NaCl via alpha-2 adrenoceptor-stimulation [6]. This glycolipid was GalNAcalpha1-3GalNAc-lipid (GN1-3GN): glycolipid production reportedly increases in humans in the hypomanic state [5, 7].
The serotonergic system maintains physical strength by regulating emotional behaviors (Figure 1). I observed that mice subjected to forced swimming stress also exhibited stress-coping behaviors in the form of motionlessness to preserve physical strength [8]. I found that this behavior was induced by a humoral glycolipid which was isolated from the fraction eluted with 100 mM NaCl via serotonergic receptor-stimulation [9]. The glycolipid is considered to be 3-O-sulfo-beta-D-galactosyl-(1->4)- N-acetyl-beta-D-glucosamine-ceramide (sG1-4GN) [10].

The cholinergic system maintains memory of stress-copings (Figure 1). The hippocampus is the chief component of the cholinergic system. Anaphylaxis induces hippocampal ischemia, and an adaptogen known as ginsenoside-Rb1 reportedly helps to cope with ischemic stress [11]. I found a humoral glycolipid preventing anaphylactic death in mice in the fraction eluted using 250 mM NaCl [12]. This humoral glycolipid protects the cholinergic module from ischemic stress in a manner similar to that of the adaptogen [13], which is considered to Fucalpha1-2[6OSO3]-Galbeta1-4Glcbeta-ceramide (sF1-2G) [10].

The dopaminergic system integrates the above-mentioned stress-coping recognition-behaviors by making them compatible with each other (Figure 1). I found a glycolipid affecting the mouse dopaminergic module from the fraction eluted with 50 mM NaCl of sera obtained from patients symptomatically diagnosed with schizophrenia [14]. Mice treated with the glycolipid showed stress-coping behaviors lacking compatibility with dopamine D2 receptor-stimulation [15]. The glycolipid was considered to be NeuAcalpha2-3Gal-lipid (Sialalpha2-3Gal-lipid): (S2-3G) [16].

Nature of the Glycolipids

The chemical structure of cerebrosides, which are found in mammalian brains, consists of a sugar chain and ceramide. Sialylcerebrosides are known as gangliosides. The humoral glycolipids, sG1-4GN, GN1-3GN and sF1-2G are cerebrosides, and S2-3G could be a ganglioside. It was previously reported that gangliosides promote synaptic plasticity [17]. The sG1-4GN, GN1-3GN, sF1-2G and S2-3G could promote synaptic plasticity in the neuronal systems. These glycolipids are coded by genes, and are probably produced in response to certain stresses. Strong stresses accelerate the secretion of gene-expressing hormones via the hypothalamus-pituitary axis. In fact, the level of cortisol differs in the brain potions of patients with schizophrenia [18].

Promotion of The Serotonergic System by a Glycolipid

The serotonergic system maintains physical strength by regulating emotional behaviors (Figure 1). I observed that mice subjected to forced swimming stress also exhibited stress-coping behaviors in the form of motionlessness to preserve physical strength [8]. I found that this behavior was induced by a humoral glycolipid which was isolated from the fraction eluted with 100 mM NaCl via serotonergic receptor-stimulation [9]. The glycolipid is considered to be 3-O-sulfo-beta-D-galactosyl-(1->4)- N-acetyl-beta-D-glucosamine-ceramide (sG1-4GN) [10].

Protection of the Cholinergic Module by a Glycolipid

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Glycolipid Promotion of the Dopaminergic Module

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Humoral Glycolipids Produced by Human Participants


Materials and Methods

Three psychiatrists symptomatically diagnosed the following patients according to the authorized criteria of the International Statistical Classification of Diseases and Related Health Problems-10 (ICD-10): 6 patients with major depression without psychotic symptoms medicated with antidepressants for 4-12weeks (DP), 6 patients with mania without psychotic symptoms medicated with lithium carbonate for 4-12weeks (MA), and 6 patients as schizophrenia presenting with psychotic symptoms medicated with atypical anti-psychotics for 4-12weeks (SZ). They did not have a history of any physical disease at the study commencement. The study also enrolled 6 healthy volunteers not suffering from psychoses. All of the participants agreed to participate in the present study, under the intensive informed consent with preservation of their anonymity and guarantee of the withdrawal agreement. The sera were pooled to emphasize interrelationship between the physical cause supposed as humoral glycolipid production and the recognition-behavioral effect indicated as symptomatic core-feature of major psychoses. Humoral glycolipids were refined by using methanol-chloroform method, the sulfate-radical was removed by using a silylating reagent, and the glycolipid production were measured with lectin-ELISA which was performed with use of a 96-well plastic plate (Sumitomo Bakelite Co., Tokyo, Japan), 5% bovine serum albumin (Sigma-Aldrich Co., St. Louis, MO, USA), biotinized-lectins recognizing terminal sugar-chain structures of the humoral glycolipids (Seikagaku Co., Tokyo, Japan), peroxidase-conjugated avidin (Seikagaku Co.), and the coloring kit (Sumitomo Bakelite Co.) [19]. The measurement was performed in 5 different plates, and the statistical difference was analyzed by a non-parametric method the Steel-Dwass test, because that difference in the measurement was not followed by normal distribution. All of these procedures were conditioned in accordance with Clinical Study Ethics Committee, Graduate School of Medicine, Akita University.

<table>
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<tr>
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<th>Blank (PS)</th>
<th>Control</th>
<th>DP</th>
<th>MA</th>
<th>SZ</th>
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<tr>
<td>sG1-4GN</td>
<td>0.044 ± 0.006</td>
<td>0.074 ± 0.005</td>
<td>0.101 ± 0.008</td>
<td>0.101 ± 0.008</td>
<td>0.107 ± 0.005</td>
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<tr>
<td>GN1-3GN</td>
<td>0.054 ± 0.004</td>
<td>0.100 ± 0.007</td>
<td>0.089 ± 0.002</td>
<td>0.114 ± 0.013</td>
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<tr>
<td>sF1-2G</td>
<td>0.045 ± 0.006</td>
<td>0.115 ± 0.014</td>
<td>0.188 ± 0.012</td>
<td>0.136 ± 0.010</td>
<td>0.137 ± 0.006</td>
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<tr>
<td>S2-3G</td>
<td>0.055 ± 0.002</td>
<td>0.074 ± 0.007</td>
<td>0.107 ± 0.013</td>
<td>0.200 ± 0.018</td>
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(Mean ± Standard Deviation), PS: physiological saline, Control: healthy volunteers, DP: major depression patients treated with antidepressants, MA: manic patients treated with lithium carbonate, SZ: schizophrenic patients treated with atypical antipsychotics, sG1-4GN: sulfated Galbeta1-4GlcNAc-lipid promoting serotonergic system, GN1-3GN: GalNAcalpha1-3GalNAc-lipid promoting adrenergic system, sF1-2G: sulfated Fucalpha1-2Gal-lipid protecting cholinergic system, S2-3G: Sialalpha2-3Gal-lipid promoting dopaminergic system, ※p<0.05 compared to Control

<table>
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<tr>
<th>Participant</th>
<th>Plate 1</th>
<th>Plate 2</th>
<th>Plate 3</th>
<th>Plate 4</th>
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<td>GN1-3GN</td>
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Raw data of light absorbance indicating the glycolipid production

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The above-described study found that the humoral glycolipids required for stress-coping were always produced by the healthy volunteers. Their glycolipid production was considered as the standard of the neuronal system activity in the recognition-behavioral stress-coping organization in humans. Antidepressants are known to increase GN1-3GN production and sG1-4GN production of mice \[9\]. The production of sG1-4GN would be decreased while the production of sF1-2G would be increased in non-medicated major depression patients. Lithium carbonate decreases GN1-3GN production of mice \[20\]. The sG1-4GN and GN1-3GN production would be higher in non-medicated mania patients. Atypical antipsychotics decrease the activities of the serotonergic neuron and dopaminergic neuron, however, the sG1-4GN and S2-3G production would be increased not only in the medicated SZ patients but also in non-medicated schizophrenia patients.

Psychiatrists have distinguished between the symptoms of major psychoses by using the phenomenological classification, i.e., ICD-10. They advocate that core-feature of major depression is loss of the motivation, decrease of emotional behaviors and obsession with the past failure, that of mania is increase of the physical activity and the eagerness, and that of schizophrenia is psychotic symptoms lacking compatibility. The serotonergic system increases emotional behaviors. The adrenergic system promotes motivation. The cholinergic system maintains memory of stress-copings. Hyperactivity of the dopaminergic system induces psychotic symptoms. These and the present findings demonstrated that the humoral glycolipid production in patients diagnosed with major depression, mania and schizophrenia is corresponding to the core-features of their symptoms, which strongly suggested that the glycolipids are considered as biomarker of major psychoses.

### Results

The participants in the control group produced sG1-4GN, GN1-3GN, sF1-2G and S2-3G. The sG1-4GN production and the sF1-2G production were increased, but, the GN1-3GN production was decreased in DP patients undergoing antidepressants treatment compared to the control group. The sG1-4GN production was increased in MA patients undergoing lithium carbonate compared to the control group. Production of the sG1-4GN was increased, while that of the S2-3G was inherently higher, in SZ patients undergoing antipsychotic anti-psychotics compared to the control group (Table 1).

### Significance of Humoral Glycolipids Produced by The Patients

The above-described study found that the humoral glycolipids required for stress-coping were always produced by the healthy volunteers. Their glycolipid production was considered as the standard of the neuronal system activity in the recognition-behavioral stress-coping organization in humans. Antidepressants are known to increase GN1-3GN production and sG1-4GN production of mice \[9\]. The production of sG1-4GN and GN1-3GN would be decreased while the production of sF1-2G would be increased in non-medicated major depression patients. Lithium carbonate decreases GN1-3GN production of mice \[20\]. The sG1-4GN and GN1-3GN production would be higher in non-medicated mania patients. Atypical antipsychotics decrease the activities of the serotonergic neuron and dopaminergic neuron, however, the sG1-4GN and S2-3G production would be increased not only in the medicated SZ patients but also in non-medicated schizophrenia patients.

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### Conclusion

Some researchers have quantitative-reasoned bio-marker of major psychoses to analyze the physiological cause, and others have qualitative-reasoned symptoms of major psychoses to evaluate the recognition-behavioral effect. I hypothesized that the recognition- behavioral stress-coping organization followed by humoral glycolipids is considered as the systemic model of major psychoses. I paid attention to core-features of major psychoses symptoms which were qualitative-reasoned via ICD-10. I quantitative-reasoned the humoral glycolipids production, and indicated that the production is corresponding to the core-feature. Finally, I concluded that the systematic model would introduce a neuroscientific view-point to major psychoses-diagnosis which has been phenomenologically performed.

### Acknowledgment

The author has no conflicts of interest to declare. The present study did not receive financial support from the public, private, or not-for-profit sectors.

### References