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Differential expression of the ghrelin-related mRNAs *GHS-R1a, GHS-R1b*, and *MBOAT4* in Japanese patients with schizophrenia

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ABSTRACT

Objectives: Ghrelin regulates appetite and also plays important roles in cognition and may be involved in vulnerability to SCZ.
Methods: In this study, we measured mRNA expression of the ghrelin-related molecules, *growth hormone secretagogue receptor 1a* (*GHS-R1a*) and *1b* (*GHS-R1b*), and the ghrelin activator, *membrane bound O-acyltransferase 4* (*MBOAT4*). Peripheral leukocytes from Japanese patients with SCZ (n = 49; 23 males, 26 females; age = 61.8 ± 13.3 years) and controls (n = 50; 25 males, 25 females; age = 62.0 ± 14.3 years) were recruited according to their clinical information. We also studied the DNA methylation rates of these genes in DNA from leukocytes.
Results: The mRNA expression of *GHS-R1a* was significantly decreased in SCZ (SCZ vs. control: 0.35 ± 0.081 vs. 1.00 ± 0.059, respectively, $p = 0.007$), but expression levels of *GHS-R1b* and *MBOAT4* were significantly increased in SCZ (SCZ vs. control: 2.02 ± 0.91 vs. 1.00 ± 0.32, $p = 0.023$, 1.37 ± 0.21 vs. 1.00 ± 0.11, respectively, $p = 0.014$). No differences in methylation rates for any genes were found.
Conclusion: We conclude that opposite expression of *GHS-R1a* and *GHS-R1b,* and elevated *MBOAT4* mRNA expression may reflect the mechanisms of SCZ.

1. Introduction

Schizophrenia is a chronic psychiatric disorder with a heterogeneous genetic and neurobiological background that influences early brain development and combination of psychotic symptoms such as hallucinations, delusions and disorganization and motivational and cognitive dysfunctions (Kahn et al., 2015). The mean lifetime prevalence of the disorder is just below 1%, but large regional differences in prevalence rates are evident owing to disparities in urbanicity and patterns of immigration (Perala et al., 2007). Prospectively designed outcome studies suggested that the course and outcome of schizophrenia is characterized by mainly unexplained heterogeneity rather than uniform poor outcome (van Os & Kapur, 2009). Several hypotheses about the pathogenesis of SCZ, such as the dopamine hypothesis (Seeman & Lee, 1975) and the glutamate hypothesis (Hu et al., 2015), have been well discussed. SCZ is characterized by positive, negative, and cognitive symptoms. Neurocognitive impairment is one of the cognitive symptoms of SCZ (Mesholam-Gately et al., 2009). A wide range of cognitive dysfunctions in the domains of language, memory, and executive functions is seen in SCZ patients (Sumiyoshi et al., 2006). The neurodevelopmental model supports that SCZ genetic and epigenetic risk factors converge on early brain development to perturb neurodevelopmental trajectories. Post-mortem studies of brain gene expression and DNA methylation suggest that risk factors for SCZ, both genetic and epigenetic variations that leave scars in the adult brain, occur principally during early brain development rather than during risk period of onset (late adolescence) (Kahn et al., 2015). Because there is evidence that genetic liability for schizophrenia is mediated in part by differential sensitivity to environments (van Os et al., 2010), endogenous hormones such as ghrelin may be involved in the pathophysiological gene-environmental interplay in schizophrenia.

Ghrelin is a well-known appetite peptide hormone that was originally identified in rodent stomach (Kojima et al., 1999). Ghrelin and its receptor genes are conserved among almost all vertebrates

Abbreviations: SCZ, schizophrenia; *GHS-R1a*, *growth hormone secretagogue receptor 1a*; *GHS-R1b*, *growth hormone secretagogue receptor 1b*; *MBOAT4*, *membrane bound O-acyltransferase 4*; GH, growth hormone; BPRS, Brief Psychiatric Rating Scale; DIEPSS, Drug-Induced Extrapyramidal Symptoms Scale

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(Gahete et al., 2014). Ghrelin is synthesized and released by gastric neuroendocrine cells and is present in various organs such as the intestine, kidney, hypothalamus, and pituitary (Gnanapavan et al., 2002).

Ghrelin is acylated by membrane bound O-acyltransferase 4 (*MBOAT4*), which is expressed in several tissues including the hippocampus (Gutierrez et al., 2008; Yang et al., 2008; Murtuza and Isokawa, 2018). Ghrelin was identified as an endogenous ligand of growth hormone (GH) secretagogue receptor 1a (*GHS-R1a*) (Howard et al., 1996). Acylated ghrelin binds to *GHS-R1a*, and deacylated ghrelin does not. Most ghrelin-regulated functions are regulated by the acylated or deacylated variants (Kojima & Kangawa, 2010). Additionally, *GHS-R1b*, which is an alternatively spliced variant of GHS-R, is a strong inhibitor of *GHS-R1a*. *GHS-R1b* dimerizes with *GHS-R1a* and has a dominant negative effect on *GHS-R1a*-mediated signaling as a direct consequence (Leung et al., 2007). Heterodimers of *GHS-R1a* and *GHS-R1b* also block *GHS-R1a* by inducing a conformational change that does not have a signaling ability (Mary et al., 2013).

GHSR mRNA expression levels are relatively high in the hypothalamus, pituitary, and hippocampus in human brain as seen with in situ hybridization (Guan et al., 1997; Gnanapavan et al., 2002). Ghrelin plays an important role in the regulation of sleep (Kluge et al., 2008), mood (Chuang and Zigman, 2010), reward (Jerlhag et al., 2009), and cognition (Andrews, 2011). Diano et al. (2006) reported that circulating ghrelin enters the hippocampus and binds to neurons in the hippocampal formation, where it promotes synapse formation at dendritic spines and generation of long-term potentiation.

Altered ghrelin secretion or signaling can contribute to the mechanism responsible for the development of schizophrenia and modification of the changes may help to reduce some symptoms of schizophrenia. However, the ghrelin levels in SCZ patients have not been well elucidated. Two studies reported that serum ghrelin levels in SCZ patients are significantly higher than in healthy persons (Birkas Kovats et al., 2005; Palik et al., 2005), but Togo et al. (2004) showed the opposite. In addition, some studies indicated a change in ghrelin levels in response to atypical antipsychotics, but their effects have not been proven (Togo et al., 2004; Himmerich et al., 2005; Murashita et al., 2005; Palik et al., 2005; Theisen et al., 2005; Hosojima et al., 2006; Esen-Danaci et al., 2008; Kim et al., 2008; Tanaka et al., 2008; Sentissi et al., 2009; Wysokiński et al., 2014).

In this study, we measured *GHS-R1a, GHS-R1b*, and *MBOAT4* mRNA expression in peripheral leukocytes of SCZ and control persons, in addition to the methylation rates of these genes.

2. Materials and methods

2.1. SCZ and control persons

SCZ persons (n = 49; 23 males, 26 females; age = 61.8 ± 13.3 years) were recruited from Ehime University Hospitals in Japan. The diagnosis of SCZ was made based on Diagnostic and Statistical Manual of Mental Disorders 5 criteria by at least two expert psychiatrists based on extensive clinical interviews and a review of medical records. Healthy control persons (n = 50; 25 males, 25 females, p = 0.762 compared to SCZ; age = 62.0 ± 14.3 years, p = 0.876) were selected from volunteers recruited from hospital staff and company employees who were documented to be free from psychiatric diseases, a history of mental illness, and psychotropic medications. SCZ symptoms were evaluated using the 18-item Brief Psychiatric Rating Scale (BPRS) (each item is scored on a scale of one to seven) (Rhoades & Overall, 1988). Antipsychotic-induced extrapyramidal symptoms were evaluated using the Drug-Induced Extrapyramidal Symptoms Scale (DIEPSS) (Inada, 2009) (Table 1).

All persons who took part in this study provided written informed consent, and the study was approved by the institutional ethics committees of Ehime University Graduate School.

Table 1
Demographic data of schizophrenia persons.

Characteristics		*GHS-R1a*	*GHS-R1b*	*MBOAT4*
N	49			
Sex (male:female)	23:26	−0.116	0.079	0.152
Age (years)	61.8 ± 13.3	0.228	−0.013	**−0.333**
Age of onset (years)	30.3 ± 12.9	0.042	−0.213	−0.218
Duration of illness (years)	31.8 ± 13.5	0.178	0.195	−0.088
CP equation	563.9 ± 358.0	−0.053	0.057	0.286
BPRS	31.0 ± 10.5	0.230	−0.149	0.001
DIEPSS	4.4 ± 3.3	0.228	0.035	−0.153
BMI (kg/m^2)	22.2 ± 5.5	0.000	0.007	0.066

The correlation between mRNA expression of *GHS-R1a, GHS-R1b* and *MBOAT4* and various parameters was evaluated with the Spearman's rank correlation coefficient. Significant difference is shown in bold ($p < 0.05$). Values are the mean ± standard deviation. Abbreviations: CP equation: chlorpromazine equivalent, BPRS: Brief Psychiatric Rating Scale, DIEPPS: Drug-Induced Extrapyramidal Symptoms Scale, BMI: body mass index.

2.2. Blood collection, total RNA isolation, and real-time PCR

We collected whole peripheral blood samples in PaxGene Blood RNA Systems tubes (BD, Tokyo, Japan) between 10:00 a.m. to 5:00 p.m. and extracted total RNA. The RNA concentration and purity were determined using absorption spectrophotometry with Nano Drop-1000 (Thermo Fisher Scientific, Yokohama, Japan). RNA (1 μg per sample) was reverse transcribed using the High-Capacity cDNA Reverse Transcription Kit (Applied Biosystems, Foster City, CA, USA) in a total volume of 40 μL. Comparative evaluation of quantitative real-time PCR was performed using TaqMan probes (Assay ID: *GHS-R1a*, Hs1026313_m1, *GHS-R1b*, Hs00269780_s1, and *MBOAT4*, Hs0174954_s1; Applied Biosystems) with the TaqMan gene expression master mix and StepOnePlus real-time PCR system (Applied Biosystems). Each sample was analyzed in duplicate.

2.3. DNA isolation and sodium bisulfite conversion of DNA

Genomic DNA was extracted from leukocytes using the QIAcube blood mini kit (Qiagen, Tokyo, Japan) and stored at 4°C. Bisulfate conversion of DNA (1 μg per sample) and subsequent purification were performed using the EpiTect Bisulfate Kit (Qiagen) and QIAcube (Qiagen) according to the manufacturer's instructions.

2.4. PCR amplification

JASPAR (http://jaspar.binf.ku.dk/) was used to identify five CpG sites in *GHSR* and two CpG sites in *MBOAT4* that were predicted to bind major transcription factors. Five sites in the *GHSR* promotor scored the highest number of transcription factors, and two CpG sites in *MBOAT4* intron 1 were predicted to bind transcription factors (predictive value > 8). These CpG sites were adjacent to the CpG sites of the hypomethylated region in the *GHSR* promotor and *MBOAT4* intron 1 (http://genome.ucsc.edu/). Primers were designed using Pyromark Assay Design software, version 2.0 (Qiagen). Fig. 1a and b show the CpG sites in the *GHSR* promotor and *MBOAT4* intron 1 and the associated transcription factors. *GHSR* primer sequences were: 5′-GGTGG GAGGGTTTTAGGGTATAT-3′ (forward) and 5′-ACTCAACCCCAAATC-3′ (reverse). *MBOAT4* primer sequences were: 5′-AGGGGGGAAGTTATTT TAAGTATAG-3′ (forward) and 5′-ACTCAAAAAAACCTAAAATTTCTCT ACC-3′ (reverse). Bisulfite-converted DNA (100 ng per 2.0 μL) was used as a template for PCR that included 0.2 mM dNTP (Applied Biosystems), 10 × PCR buffer with 15 mM $MgCl_2$ (Applied Biosystems), 0.5 U AmpliTaq gold (Applied Biosystems), and 0.2 μM forward and reverse primers (final volume 25.0 μL).

Each PCR was performed with an initial denaturation for 10 min at 94 °C, followed by 45 cycles of denaturation for 30 s at 94 °C, annealing

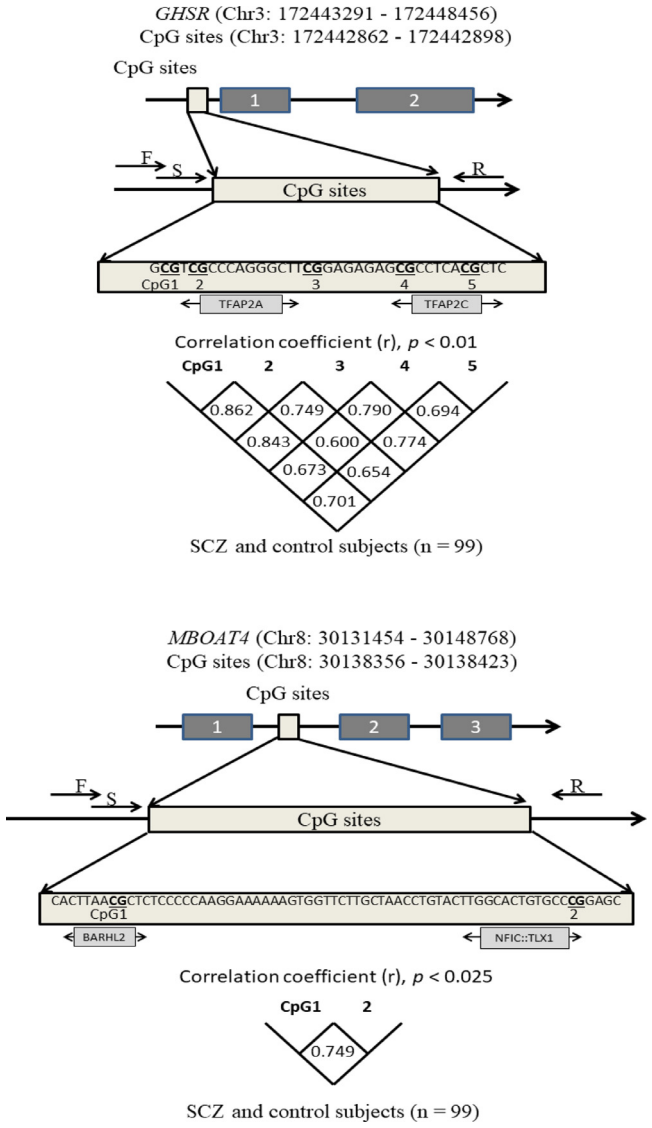

Fig. 1. Schematic diagram showing the location of the *GHSR* and *MBOAT4* regions we analyzed. CpG sites predicted to bind transcription factors (light gray boxes) are depicted under the sequence.
a: *GHSR*; Correlations between pairs of five CpGs were analyzed with the Spearman's rank correlation coefficient. Statistical significance was defined at $p = 0.01$ following Bonferroni correction.
b: *MBOAT4*; The correlation between two CpGs was analyzed with the Spearman's rank correlation coefficient. Statistical significance was defined at $p = 0.025$ following Bonferroni correction.
SCZ: schizophrenia persons, F: forward primer, R: reverse primer, S: sequencing primer.

for 30 sec at 56 °C for *GHSR* or 57 °C for *MBOAT4*, and elongation for 1 min at 72 °C, followed by a final extension at 72 °C for 10 min.

2.5. Determination of methylation rates

We analyzed each sample in duplicate. The methylation rates of each CpG site were determined by Pyromark Q24 and were accurately analyzed with PyroMark Q24 Advanced software, version 3.0.0 (Qiagen).

2.6. Statistical analysis

Statistical tests were performed using SPSS 22.0 software (IBM Japan, Tokyo, Japan). The Shapiro-Wilk test was used to determine

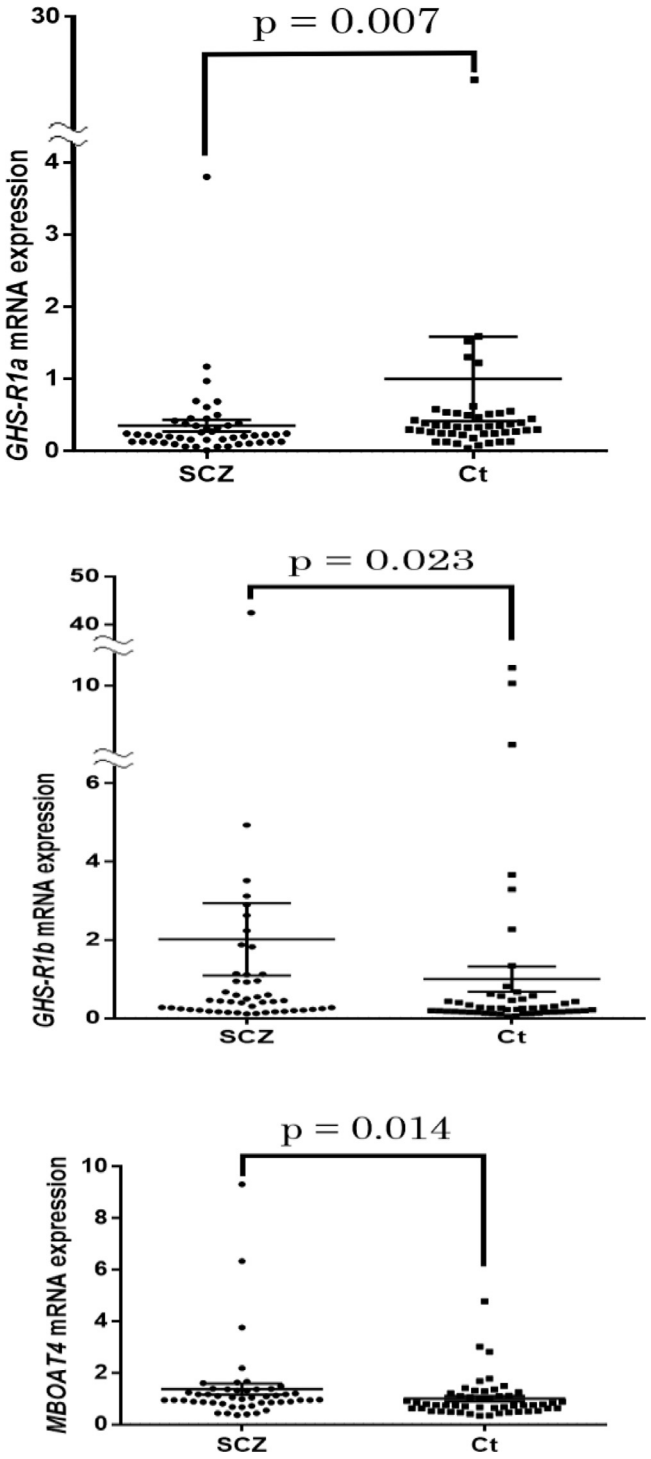

Fig. 2. **a** *GHS-R1a* mRNA expression. **b** *GHS-R1b* mRNA expression. **c** *MBOAT4* mRNA expression. The Mann-Whitney *U* test was performed to compare expression in SCZ with expression in control persons. The horizontal bar shows the mean ± standard error. SCZ: schizophrenia persons, Ct: control persons.

normality. The Mann–Whitney *U*-test with post-hoc Bonferroni correction was performed to compare the methylation rates of each CpG site between SCZ and control persons. The Fisher's exact test was performed to evaluate gender differences. Correlations between various clinical parameters and the expression levels of *GHS-R1a, GHS-R1b*, and *MBOAT4* were analyzed using the Spearman's rank correlation coefficient. $p = 0.05$ was considered statistically significant.

3. Results

3.1. GHSR: GHS-R1a and GHS-R1b, and MBOAT4 mRNA expression

GHS-R1a mRNA expression levels in peripheral leukocytes were significantly lower in SCZ patients compared with those in control persons (0.35 ± 0.081 vs. 1.00 ± 0.059, respectively, $p = 0.007$). However, *GHS-R1b* and *MBOAT4* mRNA expression levels were higher in SCZ than in controls (2.02 ± 0.91 vs. 1.00 ± 0.32, $p = 0.023$; 1.37 ± 0.21 vs. 1.00 ± 0.11, $p = 0.014$, respectively) (Fig. 2). G*Power 3 (http://www.gpower.hhu.de/) was used to calculate the power of this study (Faul et al., 2007). Consequently, the power was 0.81 (sample size: patients = 49, controls = 50, effect size = 0.6, beta/alpha ratio = 4) and was sufficient to conclude a difference (power value > 0.8). Because some outliers seemed to influence the results, we re-ran the analysis without outliers. Consequently, significant differences in *MBOAT4* (1.09 ± 0.081 vs 1.00 ± 0.108, $p = 0.029$), *GHS-R1a* (0.85 ± 0.194 vs 1.00 ± 0.122, $p = 0.011$) and *GHS-R1b* (1.79 ± 0.327 vs 1.00 ± 0.226, $p = 0.009$) were observed even after outliers (5 times higher than mean) were excluded from both patients and controls. We found no significant correlations between *GHS-R1a* or *GHS-R1b* mRNA expression and the following parameters: *GHS-R1a*: sex ($r = -0.116$, $p = 0.433$), age ($r = 0.228$, $p = 0.118$), age of onset ($r = 0.042$, $p = 0.779$), duration of illness ($r = 0.178$, $p = 0.225$), chlorpromazine (CP) equivalent ($r = -0.053$, $p = 0.725$), BPRS ($r = 0.230$, $p = 0.119$), DIEPSS ($r = 0.228$, $p = 0.124$), or body mass index (BMI) ($r = 0.00$, $p = 0.998$); *GHS-R1b*: sex ($r = 0.079$, $p = 0.595$), age ($r = -0.013$, $p = 0.932$), age of onset ($r = -0.213$, $p = 0.151$), duration of illness ($r = 0.195$, $p = 0.185$), CP equivalent ($r = 0.057$, $p = 0.705$), BPRS ($r = -0.149$, $p = 0.319$), DIEPSS ($r = 0.035$, $p = 0.815$), or BMI ($r = 0.007$, $p = 0.961$). We found a significant negative correlation between *MBOAT4* mRNA expression and age in SCZ ($p = 0.021$, $r = -0.333$) and controls ($p < 0.001$, $r = -0.592$) but not sex (SCZ: $r = 0.152$, $p = 0.302$, control: $p = 0.269$, $r = 0.159$). We found no correlations between *MBOAT4* mRNA expression and age of onset ($r = -0.218$, $p = 0.142$), duration of illness ($r = -0.088$, $p = 0.550$), CP equivalent ($r = 0.286$, $p = 0.051$), BPRS ($r = 0.001$, $p = 0.997$), DIEPSS ($r = -0.153$, $p = 0.303$), or BMI ($r = 0.066$, $p = 0.659$) (Table 1). We also found no correlations between *GHS-R1a* and *GHS-R1b* expression ($r = 0.154$, $p = 0.296$) or between *GHS-R1a* and *MBOAT4* expression ($r = 0.006$, $p = 0.970$), but we did identify a significant positive correlation between *GHS-R1b* and *MBOAT4* mRNA expression ($r = 0.665$, $p < 0.001$) in SCZ. A positive correlation between *GHS-R1b* and *MBOAT4* mRNA expression was also seen in controls (*GHS-R1a* and *GHS-R1b:* $r = 0.223$, $p = 0.115$; *GHS-R1a* and *MBOAT4:* $r = 0.017$, $p = 0.910$; *GHS-R1b* and *MBOAT4:* $r = 0.527$, $p < 0.001$).

3.2. GHSR and MBOAT4 methylation rates

We found no significant differences in *GHSR* or *MBOAT4* methylation rates between SCZ and controls (Tables 2a, 2b).

Table 2a
GHSR methylation rates.

	SCZ	Ct	*P* value
CpG1	8.9 ± 2.1	8.5 ± 1.4	0.564
CpG2	12.8 ± 2.9	12.1 ± 1.8	0.415
CpG3	26.5 ± 5.1	25.8 ± 3.4	0.543
CpG4	15.9 ± 3.2	16.1 ± 3.4	0.994
CpG5	8.9 ± 2.2	9.0 ± 2.2	0.774
Average	14.6 ± 2.8	14.3 ± 2.0	0.698

Values are the mean ± standard deviation. SCZ: schizophrenia persons, Ct: control persons.

Table 2b
MBOAT4 methylation rates.

	SCZ	Ct	*P* value
CpG1	4.7 ± 1.1	5.1 ± 1.6	0.719
CpG2	5.9 ± 2.1	5.4 ± 1.3	0.448
Average	5.3 ± 1.5	5.2 ± 1.3	0.812

Values are the mean ± standard deviation. SCZ: schizophrenia persons, Ct: control persons.

3.3. Correlation between mRNA expression of GHS-R1a, GHS-R1b, and MBOAT4 and their promoter methylation rates

We found no correlations between *GHS-R1a, GHS-R1b*, and *MBOAT4* mRNA expression and their respective promoter methylation rates. Each correlation was as follows: *GHS-R1a* (CpG1: $r = 0.171$, $p = 0.098$, CpG2: $r = 0.13$, $p = 0.21$, CpG3: $r = 0.12$, $p = 0.247$, CpG4: $r = 0.137$, $p = 0.185$, CpG5: $r = 0.065$, $p = 0.532$), *GHS-R1b* (CpG1: $r = -0.087$, $p = 0.392$, CpG2: $r = -0.036$, $p = 0.724$, CpG3: $r = -0.176$, $p = 0.083$, CpG4: $r = -0.239$, $p = 0.018$, CpG5: $r = -0.137$, $p = 0.178$), and *MBOAT4* (CpG1: $r = -0.054$, $p = 0.598$, CpG2: $r = -0.106$, $p = 0.299$, average: $r = -0.076$, $p = 0.456$).

4. Discussion

This study revealed two major findings. First, mRNA levels of *GHS-R1a* were significantly lower in SCZ than in controls. However, *GHS-R1b* and *MBOAT4* mRNA expression levels were significantly higher in SCZ than in controls. These findings suggest that lower *GHS-R1a* and elevated *GHS-R1b* and *MBOAT4* mRNA expression levels may reflect attenuation of the neuroprotective effects of ghrelin in SCZ. According to Birkás Kováts et al. (2005) and Palik et al. (2005), the serum ghrelin levels in SCZ patients are significantly higher than those in healthy persons. On the other hand, Togo et al. (2004) reported the opposite results. Although several studies reported an increase in serum ghrelin levels in response to antipsychotics (Palik et al., 2005; Murashita et al., 2005; Esen-Danaci et al., 2008; Sentissi et al., 2009), others reported no difference (Himmerich et al., 2005; Theisen et al., 2005) or a decrease (Togo et al., 2004; Hosojima et al., 2006; Kim et al., 2008; Tanaka et al., 2008; Wysokinski et al., 2014). In addition, serum ghrelin levels fluctuate with eating (Cummings et al., 2001; Tschop et al., 2001).

Ribeiro et al. (2014) proposed that ghrelin enhances cognition through *GHS-R1a*, leading to activation of the hippocampus and enhancement of excitatory synaptic transmission and synaptic plasticity by regulating gamma-amino-3-hydroxy-5-methyl-4-isoxazole propionic-type receptors. Moreover, intracerebroventricular administration of ghrelin in rats increases memory retention, indicating that ghrelin may affect these processes in the hippocampus (Carlini et al., 2002). In this study, *GHS-R1a* mRNA levels were significantly decreased in SCZ. In addition, the mRNA expression of *GHS-R1b*, which encodes a strong inhibitor of *GHS-R1a* that sustains the effects of ghrelin, was increased. However, MBOAT4 converts inactive deacylated ghrelin into active acylated ghrelin, and its mRNA levels were increased in SCZ. We suggest that in SCZ, decreased *GHS-R1a* and increased *GHS-R1b* mRNA expression levels may have contributed to the elevated *MBOAT4* mRNA expression via negative feedback to compensate for the reduced ghrelin effects that lead to reduced neuroprotection in SCZ. The significant positive correlation between *GHS-R1b* and *MBOAT4* mRNA expression levels indicates that a direct genetic relationship may exist between *GHS-R1b* and *MBOAT4*. Further studies are needed to identify the mechanism and determine whether feedback exists between them.

Second, we found a significant negative correlation between *MBOAT4* mRNA expression and age in both SCZ and controls ($r = -0.333$, $p = 0.021$; $r = -0.592$, $p < 0.001$, respectively.

Table 1). Although Paik et al. (2004) reported a negative association between total plasma ghrelin levels and age, others did not (Vilarrasa et al., 2005; Langenberg et al., 2005). However, as mentioned, ghrelin exists as active and inactive forms, and the active form binds *GHS-R1a*, which has a potent GH-releasing effect (Howard et al., 1996). Broglio et al. (2003) reported that this GH-releasing effect of ghrelin decreases with age. Thus, the negative correlation between *MBOAT4* mRNA and age is reasonable.

GHSR and *MBOAT4* methylation rates were not different between SCZ and control persons. This may have been because of two reasons. First, the most critical CpG sites of *GHSR* and *MBOAT4* may not have been identified yet. Second, other factors may affect the mRNA expression of *GHSR* and *MBOAT4*.

This study has several limitations. First, this study was performed using a relatively small sample size. Hence, our study may contain a beta error. Further studies should address this point. Second, DNA and RNA were obtained from leukocytes, and we did not discriminate expression according to cell type. CpG rates in the target regions were not significantly different among various leukocyte subsets such as neutrophils, B cells, and CD4 + T cells, using a publicly available dataset (UCSC Genome Browser; https://genome.ucsc.edu/). Influences of diurnal variation, socioeconomic status, IQ, food or physical condition (e.g., body mass index, smoking, infection and inflammation) on gene expression were not examined. We did not apply Bonferroni correction to all analysis, which may increase false positive findings. Further studies are necessary to investigate the correlation among the mRNA expression of ghrelin-related genes, methylation, and cognitive function in SCZ.

In summary, *GHS-R1a* mRNA expression levels were decreased and *GHS-R1b* and *MBOAT4* mRNA expression levels were increased in leukocytes from SCZ patients compared to controls. We found a significant correlation between *MBOAT4* mRNA expression and age in both SCZ and controls. We suggest that decreased *GHS-R1a* and increased *GHS-R1b* mRNA expression levels in peripheral leukocytes contribute to elevated *MBOAT4* mRNA expression to compensate for the reduced ghrelin effects that lead to reduced neuroprotection in SCZ. These findings suggest that disruption in ghrelin systems may be related to one of the pathological conditions of SCZ.

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Conflicts of interest

None to declare.

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