Acta Neuropsychiatrica 2015

DOI: 10.1017/neu.2015.22

ACTA NEUROPSYCHIATRICA

Effect of L-theanine on glutamatergic function in patients with schizophrenia

Ota M, Wakabayashi C, Sato N, Hori H, Hattori K, Teraishi T, Ozawa H, Okubo T, Kunugi H. Effect of L-theanine on glutamatergic function in patients with schizophrenia.

Miho Ota[1], Chisato Wakabayashi[1], Noriko Sato[2], Hiroaki Hori[1], Kotaro Hattori[1], Toshiya Teraishi[1], Hayato Ozawa[3], Tsutomu Okubo[3], Hiroshi Kunugi[1]

[1]Department of Mental Disorder Research, National Institute of Neuroscience, National Center of Neurology and Psychiatry, Tokyo, Japan; [2]Department of Radiology, National Center of Neurology and Psychiatry, Tokyo, Japan; and [3]Department of Research and Development, Nutrition Division, Taiyo Kagaku Co., Ltd, Mie, Japan

Objectives: Glutamatergic dysfunction in the brain has been implicated in the pathophysiology of schizophrenia. Previous studies suggested that L-theanine affects the glutamatergic neurotransmission and ameliorates symptoms in patients with schizophrenia. The aims of the present study were twofold: to examine the possible effects of L-theanine on symptoms in chronic schizophrenia patients and to evaluate the changes in chemical mediators, including glutamate + glutamine (Glx), in the brain by using ^{1}H magnetic resonance spectroscopy (MRS).
Method: The subjects were 17 patients with schizophrenia and 22 age- and sex-matched healthy subjects. L-Theanine (250 mg/day) was added to the patients' ongoing antipsychotic treatment for 8 weeks. The outcome measures were the Positive and Negative Syndrome Scale (PANSS), Pittsburgh Sleep Quality Index scores and MRS results.
Results: There were significant improvements in the PANSS positive scale and sleep quality after the L-theanine treatment. As for MRS, we found no significant differences in Glx levels before and after the 8 week L-theanine treatment. However, significant correlations were observed between baseline density of Glx and change in Glx density by L-theanine.
Conclusions: Our results suggest that L-theanine is effective in ameliorating positive symptoms and sleep quality in schizophrenia. The MRS findings suggest that L-theanine stabilises the glutamatergic concentration in the brain, which is a possible mechanism underlying the therapeutic effect.

Keywords: glutamine + glutamate; L-theanine (N-ethyl-L-glutamine); magnetic resonance spectroscopy; schizophrenia

Dr. Miho Ota, Department of Mental Disorder Research, National Institute of Neuroscience, National Center of Neurology and Psychiatry 4-1-1, Ogawa-Higashi, Kodaira, Tokyo 187-8502, Japan.
Tel: +81 42 341 2712;
Fax: +81 42 346 2094;
E-mail: ota@ncnp.go.jp

Accepted for publication March 18, 2015

First published online April 21, 2015

Significant outcomes

- L-Theanine ameliorated positive symptoms in schizophrenia.
- L-Theanine improved sleep quality in schizophrenia.
- L-Theanine stabilised glutamatergic concentration in the brain.

Limitations

- This was an open-label study.
- The sample size was relatively small.
- The observation period was 8 weeks; therefore, we do not know the long-term effect of L-theanine.

Introduction

Schizophrenia is a complex disorder characterised by symptoms such as delusions, hallucinations, disorganised communication, poor planning, reduced motivation, and blunted affect. *N*-methyl-D-aspartate (NMDA) receptor antagonists such as phencyclidine and ketamine induce symptoms that closely resemble those of schizophrenia, which suggests altered

NMDA-glutamatergic function in schizophrenia (1). A previous 1.5-tesla (T) ^{1}H magnetic resonance spectroscopy (MRS) study found higher levels of glutamine in the left medial prefrontal region of never-treated patients with schizophrenia compared with healthy volunteers (2). Another study using 4.0-T ^{1}H MRS found increased levels of glutamine in the left anterior cingulate and thalamic regions of never-treated, first-episode patients with schizophrenia compared to healthy volunteers (3). In addition, one study showed increased levels of Glx (glutamine + glutamate) in the medial prefrontal cortex of unmedicated patients with schizophrenia compared to controls (4). A review of ^{1}H MRS studies concerning glutamate in schizophrenia showed an overall increase in the glutamine levels of patients with schizophrenia at the early phase of the disease (5).

In contrast, a chronic schizophrenia study showed decreased levels of glutamine and glutamate in the anterior cingulate (6), and Glx in the medial prefrontal cortex (7). We found that patients with chronic schizophrenia with psychotic exacerbation showed increased Glx in the inferior parietal region (8). Although ^{1}H MRS does not selectively measure synaptic glutamate, these findings suggest that brain glutamate abnormalities may be a major neurochemical contributor to the development and exacerbation of schizophrenia.

L-Theanine (*N*-ethyl-L-glutamine) was originally found in green tea. L-Theanine accounts for ~50% of the total amino acids in green tea leaves. It comprises about 1–2% of the total dry weight of the green tea leaves, and the median amount of L-theanine per cup of green tea is 8–30 mg (9). Interestingly, L-theanine has a chemical structure that is similar to that of glutamate and affects glutamatergic neurotransmission (10–12). Growing evidence suggests that L-theanine has several psychotropic effects; our previous study revealed that L-theanine attenuated K-801-induced deficits in prepulse inhibition (PPI) in rats (13). L-Theanine improved the PPI in healthy humans (14), and several studies showed that L-theanine has an influence on mood (15–18). It was reported that L-theanine increases sleep quality and satisfaction without increasing sleep duration or causing wake-up grogginess (19,20). Among them, one schizophrenia study showed the improvement of the positive and general symptoms of schizophrenia by the administration of L-theanine (16). However, to the best of our knowledge, no study has assessed the *in vivo* effect of L-theanine on certain brain chemicals in humans.

Aims of the study

The aims of the present study were two-fold: to examine the possible effect of L-theanine on symptoms and sleep quality in chronic schizophrenia patients and to observed any changes in chemical mediators, including glutamate + glutamine, in the brain by using ^{1}H magnetic resonance spectroscopy.

Material and methods

Subjects

Data were collected between December 2011 and July 2013. Outpatients who were treated by the authors and those who voluntarily responded to our poster announcement in the Hospital were recruited. The subjects were 17 chronic schizophrenia outpatients who fulfilled the Diagnostic and Statistical Manual of Mental Disorders (4th edition) (DSM-IV) (21) criteria for schizophrenia. Additionally, 22 age- and sex-matched healthy subjects (male/female 11/11, mean age = 41.9 ± 14.9 years) were recruited from the community through local magazine advertisements and our website announcement for a study of MRS metabolites.

Research psychiatrists with board certification (M.O., H.H., and T.T.) made the diagnoses and rated the symptom severity using the Positive and Negative Syndrome Scale (PANSS) (22). Healthy subjects were interviewed for enrollment by research psychiatrists using the Japanese version of the Mini-International Neuropsychiatric Interview (23,24). Sleep quality was assessed by the Pittsburgh Sleep Quality Index (PSQI) (25). Participants were excluded if they had a history of central nervous system disease or severe head injury.

After the study was explained to the subjects, written informed consent was obtained for participation in the study from every subject. This study was approved by the Ethics Committee of the National Center of Neurology and Psychiatry, Japan.

Drug treatment and test schedule

The baseline clinical assessment (PANSS and PSQI) and MRS (scan 1) were conducted before the L-theanine treatment. Then 250 mg/day of L-theanine (Suntheanine, Taiyo Kagaku Co. Ltd, Yokkaichi, Japan) was added to ongoing antipsychotic medication for 8 weeks. The second clinical assessment and MRS (scan 2) were performed immediately after the completion of the 8-week trial. Other medications were essentially kept unchanged during the trial period.

MRS data acquisition

MR imaging was performed on a Magnetom Symphony 1.5-T (Siemens, Erlangen, Germany). Single-voxel ^{1}H spectra, recommended to use by

the widespread analysis tool 'LCModel' (26), were acquired with a point-resolved pulse sequence ('PRESS', repetition time (TR) = 1500 ms, echo time (TE) = 30 ms, 1024 points, 1000 Hz spectral width, 160 averages water-suppressed and 30 averages without water suppression) from a $1.5 \times 1.5 \times 2.5$ cm voxel placed in the left middle frontal white matter region and a $1.5 \times 2.5 \times 1.5$ cm voxel in the left inferior parietal white matter region because these are regarded as the areas associated with the psychopathology of schizophrenia (27), and because there are sufficient white matter volumes at these sites to put regions of interest (ROIs) large enough to get adequate signal-to-noise ratios. The voxels were positioned by the scanner operator based on anatomical landmarks. The scan took ~10 min per region. Voxels were placed to maximise the white matter volume and minimise grey matter and cerebrospinal fluid. Global and local shimming were performed before the ^{1}H-MRS sequence.

MRS analysis

Water-suppressed spectra were analysed using 'LCModel' (26), a fully automated, commercially available curve-fitting software program that uses a least-squares analysis method for estimating metabolite concentrations in the millimolar range. The quantification model included the following metabolites: *N*-acetylaspartate (NAA), Glx, inositol, and glycerophosphocholine + phosphocholine. For each spectrum, the area under each peak was normalised to the unsuppressed water peak (corrected for water T1 relaxation) (28), yielding metabolite concentrations. The fitting quality of each spectrum is shown as the per cent standard deviation (SD), and those with SD values over 20% were excluded from analysis.

Statistical analysis

The differences in PANSS and PSQI scores between before and after the L-theanine treatment were compared using the paired *t*-test. We evaluated the differences in the metabolic concentrations of NAA, Glx, inositol and glycerophosphocholine + phosphocholine in the left frontal and inferior parietal white matter in schizophrenic patients before and after the L-theanine treatment using paired *t*-tests. With respect to Glx, we calculated the % ratio of the Glx levels before and after the L-theanine treatment, then analysed the effects of the L-theanine treatment by partial correlation using the age and sex as covariates. We calculated the % ratio by the formula:

$$\%\,\text{ratio} = \text{Glx in scan 2}/\text{Glx in scan 1}.$$

We also evaluated the relationships between the Glx levels and the psychiatric symptoms and the antipsychotic medication by generalised estimating equations using the Glx as dependent variable, and the dose of antipsychotic drug and PANSS score as covariates.

Statistical analyses were performed using the SPSS Statistics for Windows 22.0 software program (SPSS Japan, Tokyo, Japan).

Results

Nine male and eight female outpatients with chronic schizophrenia participated in this study. Their mean age was 40.6 ± 12.3 years and their mean education years were 13.4 ± 2.1. The mean chlorpromazine equivalent dose of antipsychotic medication was 958.5 ± 516.6 mg/day (29,30). The results of the clinical assessments, MRS data before and after L-theanine treatment and the MRS data of the healthy subjects are shown in Table 1. There were significant

Table 1. Clinical characteristics of the schizophrenic patients

		Scan 1	Scan 2	*p*-value	Healthy subjects
	PANSS total	62.7 ± 11.8	56.5 ± 11.1	0.03*	
	PANSS positive	14.6 ± 4.3	12.2 ± 3.5	0.025	
	PANSS negative	16.1 ± 4.8	14.6 ± 4.0	0.051	
	PANSS general	31.9 ± 6.5	29.7 ± 6.4	0.19	
	PSQI total score	7.8 ± 3.4	6.2 ± 2.5	0.008*	
MRS data					
Left frontal WM	NAA (digit scale)	4.8 ± 0.5	4.5 ± 0.6	0.11	5.0 ± 0.6
	Inositol (digit scale)	3.2 ± 0.7	2.9 ± 0.8	0.18	3.2 ± 0.6
	Glutamine + Glutamate (Glx) (digit scale)	6.8 ± 1.1	6.6 ± 1.2	0.66	7.0 ± 1.3
	Glycerophosphocholine + Phosphocholine (digit scale)	1.3 ± 0.2	1.3 ± 0.2	0.52	1.2 ± 0.2
Left parietal WM	NAA (digit scale)	5.3 ± 0.7	5.3 ± 0.6	0.99	5.8 ± 0.3
	Inositol (digit scale)	3.2 ± 0.5	3.1 ± 0.5	0.52	3.1 ± 0.5
	Glutamine + Glutamate (Glx) (digit scale)	6.9 ± 0.9	7.2 ± 0.9	0.32	6.5 ± 0.9
	Glycerophosphocholine + Phosphocholine (digit scale)	1.2 ± 0.1	1.2 ± 0.1	0.97	1.3 ± 0.2

MRS, magnetic resonance spectroscopy; NAA, N-acetyl-aspartate; PANSS, Positive and Negative Syndrome Scale; WM, white matter.

* Significant difference between pre- and post-treatment after multiple comparisons.

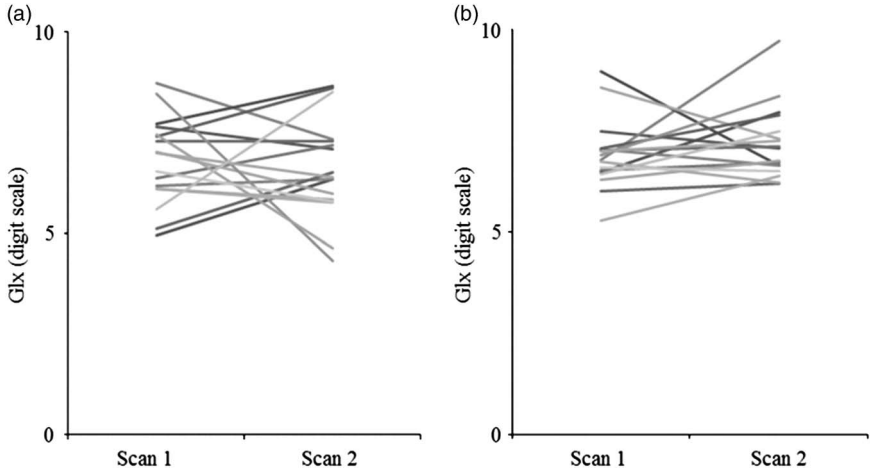

Fig. 1. Relation between the glutamate + glutamine (Glx) in scans 1 and 2. There were no significant differences in Glx between scans 1 and 2 in the frontal region (a) or the inferior parietal region (b).

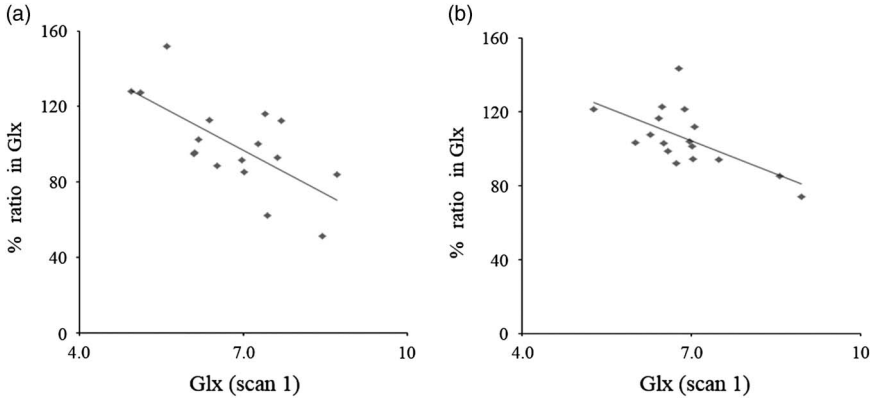

Fig. 2. Relations between glutamate + glutamine (Glx) in scan 1 and the % ratio for Glx after 8-week L-theanine treatment. There were significant negative correlations between Glx at the baseline (scan 1) and the % ratio in Glx following the L-theanine treatment in the frontal (a) and inferior parietal (b) regions.

differences in the PANSS total score ($t = 2.38$, $p = 0.030$) and the PSQI total score ($t = 3.01$, $p = 0.008$) between pre- and post-treatment with L-theanine. With respect to the PANSS scores, we found a nominal improvement in the positive score after the 8-week administration of L-theanine ($t = 2.47$, $p = 0.025$; Table 1).

As for MRS data, there were no significant differences in any metabolite between scans 1 and 2 (Fig. 1; Table 1). The relationships between Glx in scan 1 and the % ratio for Glx after the L-theanine treatment are shown in Fig. 2. There were significant negative correlations between Glx at baseline and the % ratio for Glx at the frontal ($p = 0.003$, partial correlation coefficient $= -0.72$) and inferior parietal ($p = 0.010$, partial correlation coefficient $= -0.64$) regions. We found no relationships between the Glx in the frontal and parietal regions and the clinical characteristics (Table 2).

Table 2. Estimated effects of clinical characteristics on glutamate + glutamine

			95% Wald confidence interval	
Region	Parameter	Estimated value	Lower	Upper
Frontal	Antipsychotics*	0.000	−0.001	0.001
	PANSS total	0.014	−0.020	0.047
Parietal	Antipsychotics*	0.000	−0.001	0.001
	PANSS total	−0.015	−0.047	0.016

PANSS, the Positive and Negative Syndrome Scale.
* Chlorpromazine equivalent dose.

Discussion

We found that the 8-week add-on L-theanine treatment significantly reduced the PANSS scores in schizophrenia patients who were under treatment with antipsychotic medication. MRS revealed that L-theanine affected the concentration of Glx in the

frontal and inferior parietal regions. Interestingly, there were significant negative correlations between Glx at baseline and the % ratio in Glx at the frontal and inferior parietal regions. To our knowledge, this is the first study that obtained evidence of the effect of L-theanine on Glx, which is related to glutamatergic neurotransmission in humans.

The therapeutic effects of L-theanine against the schizophrenic symptoms observed in the present study are consistent with those of previous studies (16,17). In addition, our finding of a positive effect of L-theanine on sleep supports the results of preceding studies (19,20).

L-Theanine, which has a chemical structure that is similar to that of glutamate, affects glutamatergic neurotransmission (10–12). The effects of L-theanine on schizophrenia symptoms and Glx concentrations in the brain observed in the present study might be attributable to its chemical structure. It is known that L-theanine has weak affinities for kainate, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid, and NMDA receptors (10,31). On the other hand, L-theanine was reported to be able to suppress the excitotoxic release of glutamate derived from the Gln/glutamate cycle through the inhibition of Gln incorporation in glutamatergic neurons in a particular situation (12).

In a previous study, we focused on the effect of L-theanine on PPI, a measure of sensorimotor gating that is known to be impaired in schizophrenia (32,33), and we observed the enhancement of PPI at particular doses of L-theanine (14). It is possible that L-theanine exerts its effects, at least in part, through a partial agonistic-like action on the glutamatergic system. Another study evaluated the dopamine synthesis capacities at resting condition and after the oral administration of a single dose of the partial agonist antipsychotic aripiprazole, revealing a significant negative correlation between the baseline and aripiprazole-induced changes in dopamine synthesis capacities (34). These findings suggested that aripiprazole may have a stabilising effect on the dopamine synthesis capacity. Similarly, L-theanine may have a stabilising effect on the glutamatergic neurotransmission.

Several studies examined glutamatergic changes in first-episode schizophrenia (2,3,35), chronic schizophrenia (6–8,36,37), and individuals at high risk for schizophrenia (38). The results obtained at each clinical stage and the clinical severity indicate that the glutamatergic metabolites of schizophrenia change in a course-dependent manner. L-Theanine was shown to be a safe and well-tolerated medication (16), and the stabilising effect of L-theanine on glutamatergic neurotransmission could be of significant benefit in clinical practice.

The present study has several limitations. First, this was an open-label study and thus subject to bias in clinical assessments, although the MRS findings are free from such bias. Second, the sample size was relatively small, and thus subject to type II errors. Our results reached statistical significance, however, future studies with larger numbers of subjects are necessary to verify the present findings. Thirdly, the observation period was only 8 weeks and we therefore do not yet know the long-term effects of L-theanine.

Acknowledgement

This research was funded by an unrestricted research grant provided by the Taiyo Life Insurance Himawari Foundation, Tokyo, Japan. Contributors: M. Ota designed the study and wrote the first draft of the manuscript. H. Hori, K. Hattori and T. Teraishi collected the data. C. Wakabayashi, N. Sato, H. Ozawa, T. Okubo and H. Kunugi managed the analyses. All authors contributed to and have approved the final manuscript.

Conflicts of Interest

This research was funded by an unrestricted research grant provided by the Taiyo Life Insurance Himawari Foundation, Tokyo, Japan. H.O. and T.O. were the employees of Taiyo Kagaku Co. Ltd.; however, they only contributed to inform the other authors about L-theanine and to offer the supplement tablets. They did not analyse the clinical data or manage the analysis. This clinical study was registered in the UMIN Clinical Trials Registry (registration date 12/26/2011, registration no. 20111226-234711).

Supplementary material

To view supplementary material for this article, please visit http://dx.doi.org/10.1017/neu.2015.22

References

1. Tsai G, Van Kammen DP, Chen S, Kelley ME, Grier A, Coyle JT. Glutamatergic neurotransmission involves structural and clinical deficits of schizophrenia. Biol Psychiatry 1998;**44**:667–674.
2. Bartha R, Williamson PC, Drost DJ et al. Measurement of glutamate and glutamine in the medial prefrontal cortex of never-treated schizophrenic patients and healthy controls using proton magnetic resonance spectroscopy. Arch Gen Psychiatry 1997;**54**:959–965.
3. Théberge J, Bartha R, Drost DJ et al. Glutamate and glutamine measured with 4.0 T proton MRS in never-treated patients with schizophrenia and healthy volunteers. Am J Psychiatry 2002;**159**:1944–1946.
4. Kegeles LS, Mao X, Stanford AD et al. Elevated prefrontal cortex γ-aminobutyric acid and glutamate-glutamine levels in schizophrenia measured in vivo with proton magnetic resonance spectroscopy. Arch Gen Psychiatry 2012;**69**:449–459.

5. Marsman A, Van Den Heuvel MP, Klomp DW, Kahn RS, Luijten PR, Hulshoff Pol HE. Glutamate in schizophrenia: a focused review and meta-analysis of 1 h-MRS studies. Schizophr Bull 2013;**39**:120–129.
6. Théberge J, Al-Semaan Y, Williamson PC et al. Glutamate and glutamine in the anterior cingulate and thalamus of medicated patients with chronic schizophrenia and healthy comparison subjects measured with 4.0-T proton MRS. Am J Psychiatry 2003;**160**:2231–2233.
7. Natsubori T, Inoue H, Abe O et al. Reduced frontal glutamate + glutamine and n-acetylaspartate levels in patients with chronic schizophrenia but not in those at clinical high risk for psychosis or with first-episode schizophrenia. Schizophr Bull 2014;**40**:1128–1139.
8. Ota M, Ishikawa M, Sato N et al. Glutamatergic changes in the cerebral white matter associated with schizophrenic exacerbation. Acta Psychiatr Scand 2012;**126**:72–78.
9. De Mejia EG, Ramirez-Mares MV, Puangpraphant S. Bioactive components of tea: cancer, inflammation and behavior. Brain Behav Immun 2009;**23**:721–731.
10. Nathan PJ, Lu K, Gray M, Oliver C. The neuropharmacology of L-theanine (*N*-ethyl-L-glutamine): a possible neuroprotective and cognitive enhancing agent. J Herb Pharmacother 2006;**6**:21–30.
11. Kakuda T, Nozawa A, Sugimoto A, Niino H. Inhibition by theanine of binding of [3H]AMPA, [3H]kainate, and [3H] MDL 105,519 to glutamate receptors. Biosci Biotechnol Biochem 2002;**66**:2683–2686.
12. Kakuda T, Hinoi E, Abe A, Nozawa A, Ogura M, Yoneda Y. Theanine, an ingredient of green tea, inhibits [3H]glutamine transport in neurons and astroglia in rat brain. J Neurosci Res 2008;**86**:1846–1856.
13. Wakabayashi C, Numakawa T, Ninomiya M et al. Behavioral and molecular evidence for psychotropic effects in L-theanine. Psychopharmacology (Berl) 2012;**219**:1099–1109.
14. Ota M, Wakabayashi C, Matsuo J et al. Effect of L-theanine on sensorimotor gating in human subjects. Psychiatry Clin Neurosci 2013;**68**:337–343.
15. Lu K, Gray MA, Oliver C et al. The acute effects of L-theanine in comparison with alprazolam on anticipatory anxiety in humans. Hum Psychopharmacol 2004;**19**:457–465.
16. Ritsner MS, Miodownik C, Ratner Y et al. L-Theanine relieves positive, activation, and anxiety symptoms in patients with schizophrenia and schizoaffective disorder: an 8-week, randomized, double-blind, placebo-controlled, 2-center study. J Clin Psychiatry 2011;**72**:34–42.
17. Miodownik C, Maayan R, Ratner Y et al. Serum levels of brain-derived neurotrophic factor and cortisol to sulfate of dehydroepiandrosterone molar ratio associated with clinical response to L-theanine as augmentation of antipsychotic therapy in schizophrenia and schizoaffective disorder patients. Clin Neuropharmacol 2011;**34**:155–160.
18. Unno K, Tanida N, Ishii N et al. Anti-stress effect of theanine on students during pharmacy practice: positive correlation among salivary α-amylase activity, trait anxiety and subjective stress. Pharmacol Biochem Behav 2013;**111**:128–135.
19. Lyon MR, Kapoor MP, Juneja LR. The effects of L-theanine (Suntheanine®) on objective sleep quality in boys with attention deficit hyperactivity disorder (ADHD): a randomized, double-blind, placebo-controlled clinical trial. Altern Med Rev 2011;**16**:348–354.
20. Ozeki M, Juneja LR, Shirakawa S. The effects of theanine on sleep with the actigraph as physiological indicator. Jpn J Physiol Anthropol 2004;**9**:143–150.
21. American Psychiatric Association. DSM-IV: diagnostic and statistical manual of mental disorders, 4th edn. Washington, DC: American Psychiatric Press Inc, 1994.
22. Kay SR, Opler LA, Fiszbein A. Positive and Negative Syndrome Scale (PANSS) manual. Schizophr Bull 1987;**13**: 261–276.
23. Otsubo T, Tanaka K, Koda R et al. Reliability and validity of Japanese version of the mini-international neuropsychiatric interview. Psychiatry Clin Neurosci 2005;**59**:517–526.
24. Sheehan DV, Lecrubier Y, Sheehan KH et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry 1998;**59**:22–57.
25. Buysse DJ, Reynolds CF 3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh sleep quality index: a new instrument for psychiatric practice and research. Psychiatry Res 1989;**28**:193–213.
26. Provencher SW. Estimation of metabolite concentrations from localized in vivo proton NMR spectra. Magn Reson Med 1993;**30**:672–679.
27. Rowland LM, Spieker EA, Francis A, Barker PB, Carpenter WT, Buchanan RW. White matter alterations in deficit schizophrenia. Neuropsychopharmacology 2009;**34**:1514–1522.
28. Barker PB, Soher BJ, Blackband SJ, Chatham JC, Mathews VP, Bryan RN. Quantitation of proton NMR spectra of the human brain using tissue water as an internal concentration standard. NMR Biomed 1993;**6**:89–94.
29. American Psychiatric Association. Practice guidelines for the treatment of patients with schizophrenia. Washington, DC: American Psychiatric Press Inc., 1997.
30. Inagaki A, Inada T. Dose equivalence of psychotropic drugs. part x viii: dose equivalence of psychotropic drugs: 2006-version. Jpn J Clin Psychopharmacol 2006;**9**:1443–1447.
31. Yokogoshi H, Terashima T. Effect of theanine, r-lutamylethylamide, on brain monoamines, striatal dopamine release and some kinds of behaviour in rats. Nutrition 2000;**16**:776–777.
32. Braff DL, Geyer MA. Sensorimotor gating and schizophrenia. Human and animal model studies. Arch Gen Psychiatry 1990;**47**:181–188.
33. Kunugi H, Tanaka M, Hori H, Hashimoto R, Saitoh O, Hironaka N. Prepulse inhibition of acoustic startle in japanese patients with chronic schizophrenia. Neurosci Res 2007;**59**:23–28.
34. Ito H, Takano H, Arakawa R et al. Effects of dopamine D2 receptor partial agonist antipsychotic aripiprazole on dopamine synthesis in human brain measured by PET with L-[β-11C]DOPA. PLoS One 2012;**7**:e46488.
35. Théberge J, Williamson KE, Aoyama N et al. Longitudinal grey-matter and glutamatergic losses in first-episode schizophrenia. Br J Psychiatry 2007;**191**:325–354.
36. Van Elst LT, Valerius G, Büchert M et al. Increased prefrontal and hippocampal glutamate concentration in schizophrenia: evidence from a magnetic resonance spectroscopy study. Biol Psychiatry 2005;**58**:724–730.
37. Pakkenberg B, Scheel-Kruger J, Kristiansen LV. Schizophrenia; from structure to function with special focus on the mediodorsal thalamic prefrontal loop. Acta Psychiatr Scand 2009;**120**:345–354.
38. Tibbo P, Hanstock C, Valiakalayil A, Allen P. 3-T proton MRS investigation of glutamate and glutamine in adolescents at high genetic risk for schizophrenia. Am J Psychiatry 2004;**161**:1116–1118.