Glycative Stress Research

Online edition : ISSN 2188-3610
Print edition : ISSN 2188-3602
Received : July 31, 2018
Accepted : August 24, 2018
Published online : September 30, 2018
doi:10.24659/gsr.5.3_147

Review article

Glycative stress and anti-aging: 9. Glycative stress and schizophrenia.

Masayuki Yagi, Yoshikazu Yonei

Anti-Aging Medical Research Center and Glycative Stress Research Center, Faculty of Life and Medical Sciences, Doshisha University, Kyoto, Japan

Abstract

Schizophrenia is a mental disease characterized by hallucination and delusion; its clinical conditions have many unclear points. There are dopamine hypothesis, glutamate hypothesis and protein posttranslation modification for schizophrenia. Protein posttranslation modification means that phosphorylation, ubiquitination, methylation and glycosylation after protein synthesis are involved in clinical conditions of schizophrenia. In schizophrenia, there is a multiplex family with a frameshift mutation of the glyoxalase 1 (GLO1) gene existing in the No. 6 chromosome. In the blood of the patient in this case, the concentration of pentosidine, a kind of advanced glycation end products (AGEs), increased and vitamin B6 having carbonyl scavenging activities decreased, compared with those of healthy people. Therefore, it is thought that schizophrenia is a condition where glycative stress has been enhanced. In patients with carbonyl stress-induced schizophrenia, a decrease of vitamin B6 in their blood is observed; therefore, the effectiveness of vitamin B6 replacement therapy can be expected. Clinical trials of the administration of pyridoxiamine to patients with schizophrenia suggest the possible effectiveness of this therapy.

***KEY WORDS*:** glyoxalase 1, carbonylation, pyridoxiamine, pentosidine

1. Introduction: What is Schizophrenia?

Schizophrenia is a mood disorder similar to major depressive disorder and bipolar disorder. It is characterized by symptoms such as hallucination and delusion. In this case, functions of managing family and social lives while communicating with other people are damaged, and the patients become unable to reflect on themselves and understand that "their feeling, thinking and behavior are distorted because of disease." Progress of the disease is likely to follow a chronic process, during that time, an acute stage appears where hallucination and delusion become strong. According to a 2014 survey of patients by the Ministry of Health and Welfare, the number of patients with mental disease admitted in hospital was 266,000. Among those, the number of patients with schizophrenia, schizophrenic disorder and delusional disorder was 166,000[1]. The reasons why the general recognition of schizophrenia is low are that its symptoms are difficult to be discerned, that it is subjected to social prejudice and that its only treatment is conservative pharmacotherapy.

Although there are many unclear points in clinical conditions of schizophrenia, it is known that it has dopamine hypothesis, glutamate hypothesis and protein posttranslation modification[2,3]. Dopamine hypothesis is that the over activity of the subcortical dopamine nerve function accompanied by the low activity of the dopamine nerve function in the frontal cortex is involved in clinical conditions of schizophrenia. Glutamate hypothesis is that the dysfunction of glutamatergic neurotransmission is involved in clinical conditions of schizophrenia. Protein posttranslation modification is that phosphorylation, ubiquitination, methylation and glycosylation after protein synthesis are involved in clinical conditions of schizophrenia. It is already understood that irreversible changes such as oxidation, carbonylation, glycation and nitration of *in vivo* protein are involved in the onset and progressions of various disorders[4].

Contact Address: Professor Masayuki Yagi, PhD
Glycative Stress Research Center,
Faculty of Life and Medical Sciences, Doshisha University
1-3 Tatara Miyakodani, Kyotanabe, Kyoto, 610-0394 Japan
Phone/Fax: +81-774-65-6394 Email: myagi@mail.doshisha.ac.jp
Co-author: Yonei Y, yyonei@mail.doshisha.ac.jp

2. Schizophrenia and Glycative Stress

Many cases of the involvement of No. 6 chromosome in schizophrenia have been reported [5]. An enzyme gene called glyoxalase 1 (GLO1) exists in this chromosome. Glyoxalase decomposes carbonyl compounds resulting from oxidant stress and glycative stress. Among *in vivo* carbonyl compounds, there are methylglyoxsal, glyoxsal and 3-deoxyglucosone generated from glucose and lipids. They are also glycation reaction intermediates. As they modify protein and generate advanced glycation end products (AGEs), they are the substances responsible for glycative stress. The condition where protein modifications such as AGEs are progressed by carbonyl compounds is also called carbonyl stress.

The frameshift mutation is found in the GLO1 gene of patients with carbonyl stress-induced schizophrenia. Therefore, it was found that the expression of GLO1, of the patient in this case, fell to 50% of that of healthy people [5]. This was derived via the analysis of DNA of an individual of a multiplex family with schizophrenia. It is reported that the concentration of pentosidine, one of AGEs, in the blood of the patient of this case increased up to 3.7 times of the comparison subject. The concentration of vitamin B6 with carbonyl scavenging activities *in vivo*, similar to glyoxalase, decreased to 20% lower than in a healthy person [3, 6]. Furthermore, on the survey of patients with schizophrenia without diabetes, a kidney problem or an inflammatory disorder, it was confirmed that the concentration of pentosidine in blood significantly rose and that of vitamin B6 significantly fell (***Fig. 1***) [6].

Furthermore, the increase of an accumulation of skin AGEs [7] and the increase of argpyrimidine, an AGE derived from methylglyoxal, in 56-KDa protein in red cells [8] were reported for patients with schizophrenia. Therefore, it can be said that schizophrenia is the result of progressed symptoms of glycative stress.

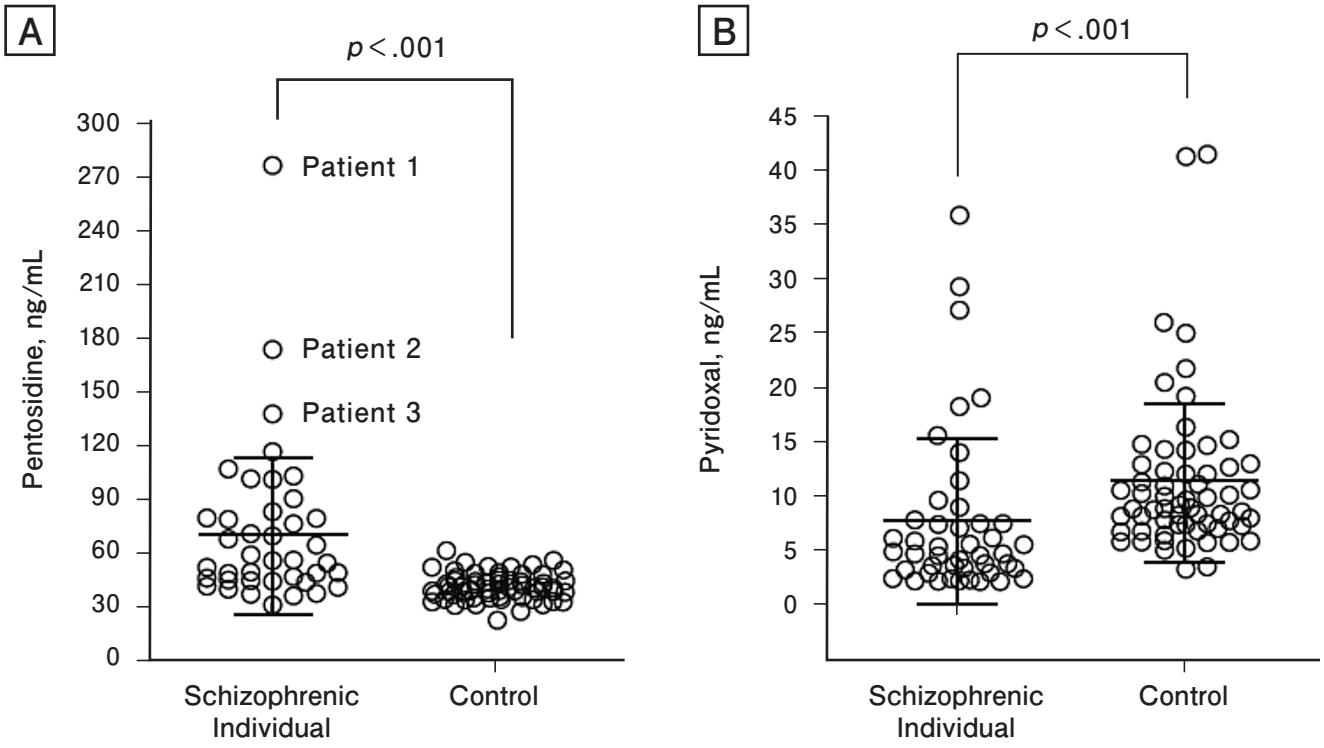

Fig. 1. **Plasma pentosidine accumulation and serum pyridoxal (vitamin B6) depletion.**

Levels of plasma pentosidine (**A**) and serum pyridoxal (**B**) were analyzed using high-performance liquid chromatography techniques. Values were compared using the Mann-Whitney U test (2-tailed). Error bars indicate standard deviations. The figure is adapted from Reference 6.

3. Possibility of Schizophrenia Treatment by Inhibiting Glycative Stress

A decrease of vitamin B6 in blood is recognized in patients with carbonyl stress-induced schizophrenia, so the effectiveness of vitamin B6 replacement therapy can be expected. There are three substances of pyridoxine, pyridoxal and pyridoxiamine in vitamin B6 and they are in parallel relationship in solution. Pyridoxiamine among them has carbonyl scavenging activities[9]. Pyridoxiamine inhibits the formation of carbonyl compounds caused by glycation and oxidization *in vivo*, therefore, the improvement of schizophrenia can be expected (***Fig. 2***)[10]. There is a report of clinical testing of pyridoxiamine administration for patients with schizophrenia. As the result of the administration of pyridoxiamine 1,200-2,400 mg per day for 24 weeks to the patients with schizophrenia with a high concentration value of pentosidine in their blood, the concentration of the pentosidine in their blood decreased by 26.8%. In the case of patients presenting typical carbonyl stress with frameshift mutation in the GLO1 enzyme, pentosidine decreased and their psychological symptoms improved[11]. Therefore, it is presumed that therapy by administration of pyridoxiamine to the patients with schizophrenia accompanied by carbonyl stress is very effective.

Acknowledgement

This work was partially supported by the Japanese Council for Science, Technology and Innovation, SIP (Project ID 14533567), "Technologies for creating next-generation agriculture, forestry and fisheries" (funding agency: Bio-oriented Technology Research Advancement Institution, NARO).

Conflict of Interest Statement

The authors claim no conflict of interest in this study.

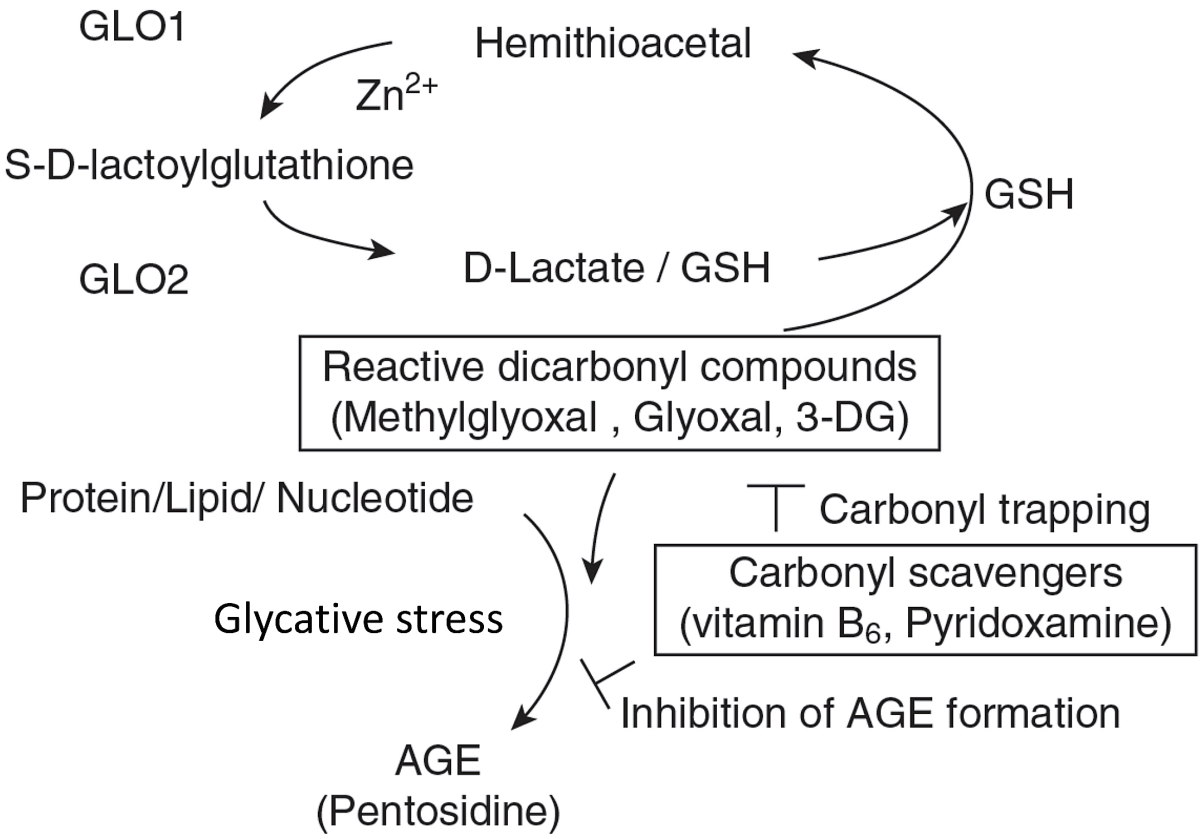

Fig. 2. **Glyoxalase detoxification system and glycative stress.**

Accumulation of reactive carbonyl compounds results in modification of proteins and the eventual formation of advanced glycation end products (AGEs) and methylglyoxal-adducts. Glyoxalase proteins are ubiquitously expressed in various tissues, including the brain, and provide an effective defense against the accumulation of reactive dicarbonyl compounds. Vitamin B6 also detoxifies reactive carbonyl compounds by trapping these products and/or by inhibiting the formation of AGEs. GLO1, glyoxalase 1; GLO2, glyoxalase 2; GSH, glutathione. The figure is adapted and modified from Reference 10.

Reference

1) 2014 Summary of Patient Survey. Ministry of Health, Labour and Welfare Japan. https://www.mhlw.go.jp/toukei/saikin/hw/kanja/14/dl/kanja.pdf (in Japanese)
2) Howes O, McCutcheon R, Stone J. Glutamate and dopamine in schizophrenia: An update for the 21st century. J Psychopharmacol. 2015; 29: 97-115.
3) Arai M, Miyashita M, Ichikawa T, et al. Carbonyl stress-related schizophrenia: Perspective on future therapy and hypotheses regarding pathophysiology of schizophrenia. Psychiatria et Neurologia Japonica. 2012; 114: 199-208. (in Japanese)
4) Jaisson S, Gillery P. Evaluation of nonenzymatic posttranslational modification-derived products as biomarkers of molecular aging of proteins. Clin Chem. 2010; 56: 1401-1412.
5) Turecki G, Rouleau GA, Joober R, et al. Schizophrenia and chromosome 6p. Am J Med Genet. 1997; 74: 195-198.
6) Arai M, Yuzawa H, Nohara I, et al. Enhanced carbonyl stress in a subpopulation of schizophrenia. Arch Gen Psychiatry. 2010; 67: 589-597.
7) Kouidrat Y, Amad A, Desailloud R, et al. Increased advanced glycation end-products (AGEs) assessed by skin autofluorescence in schizophrenia. J Psychiatr Res. 2013; 47: 1044-1048.
8) Ishida YI, Kayama T, Kibune Y, et al. Identification of an argpyrimidine-modified protein in human red blood cells from schizophrenic patients: A possible biomarker for diseases involving carbonyl stress. Biochem Biophys Res Commun. 2017; 493: 573-577.
9) Voziyan PA, Thomas O. Metz TO, et al. A post-Amadori inhibitor pyridoxamine also inhibits chemical modification of proteins by scavenging carbonyl intermediates of carbohydrate and lipid degradation. J Biol Chem. 2002; 277: 3397-3403.
10) Arai M, Miyashita M, Kobori A, et al. Carbonyl stress and schizophrenia. Psychiatry Clin Neurosci. 2014; 68: 655-665.
11) Itokawa M, Miyashita M, Arai M, et al. Pyridoxamine: A novel treatment for schizophrenia with enhanced carbonyl stress. Psychiatry Clin Neurosci. 2018; 72: 35-44.