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Review

Advanced glycation end products and schizophrenia: A systematic review

Youssef Kouidrat [a, b, *], Ali Amad [c], Makoto Arai [d], Mitsuhiro Miyashita [d], Jean-Daniel Lalau [a], Gwenole Loas [e], Masanari Itokawa [d]

[a] Department of Endocrinology, University of Picardie-Jules Verne, CHU d'Amiens, Amiens, France
[b] Department of Nutrition, Hôpital Maritime de Berck, Assistance Publique-Hôpitaux de Paris (AP-HP), 62600 Berck-sur-Mer, France
[c] King's College London, Institute of Psychiatry, Psychology and Neuroscience, London, UK
[d] Project for Schizophrenia and Affective Disorder Research, Tokyo Metropolitan Institute of Medical Science, Tokyo, Japan
[e] Department of Psychiatry, Erasme Hospital, ULB, 1070 Bruxelles, Belgium

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ABSTRACT

Oxidative stress has become an exciting area of research on schizophrenia, which is a highly prevalent condition that affects approximately 1% of the worldwide population. Advanced glycation end products (AGEs), which are considered metabolic biomarkers of increased oxidative stress, have a pathogenic role in the development and progression of different oxidative stress-based diseases including atherosclerosis, diabetes, neurodegenerative disorders and schizophrenia. AGE formation and accumulation as well as the activation of its receptor (RAGE) can lead to signaling through several inflammatory signaling pathways and further damaging effects. This systematic review is based on a search conducted in July 2014 in which 6 studies were identified that met our criteria. In this work, we describe how recent methodological advances regarding the role of AGEs may contribute to a better understanding of the pathophysiology of schizophrenia and provide a different approach in the comprehension of the relationship between cardiovascular disease and schizophrenia. These latest findings may lead to new directions for future research on novel diagnostic and treatment strategies.

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1. Introduction

Schizophrenia is a severe mental disease with a prevalence of 1% worldwide. Schizophrenia is characterized by a wide range of symptoms, including positive symptoms (delusions and hallucinations), negative symptoms (social withdrawal, anhedonia), cognitive symptoms (difficulties with memory and attention) and affective dysregulation (van Os and Kapur, 2009). Despite extensive research, its pathophysiology remains unclear. However, significant advances have been made in identifying genetic and key biochemical systems involved in the disease and suggest that oxidative stress contributes to the pathophysiology of schizophrenia (Emiliani et al., 2014; Itokawa et al., 2014; Kulak et al., 2013; Wu et al., 2013).

Oxidative stress is defined as an imbalance between pro-oxidant, such as reactive oxygen species (ROS), and antioxidant systems which ultimately leads to cellular damage. Furthermore, oxidative stress is a central mediator of AGEs (advanced glycation end-products) formation. AGEs are a heterogenous class of biomolecules formed by non-enzymatic glycation and oxidation of proteins and/or lipids. This process is an endogenous process in which reducing sugars react with amino groups in proteins through a series of Maillard reactions (Vistoli et al., 2013). This process results in alterations of protein structure and function in cells and body tissues. Moreover, AGEs interact with the receptor for AGEs (RAGE) and induce increased oxidative stress and inflammatory mediators (Ott et al., 2014; Vistoli et al., 2013). Pentosidine, carboxy-ethyl-lysine (CEL), and carboxy-methyl-lysine (CML) are examples of AGEs.

Several studies indicate that the accumulation of AGEs has been implicated in the development and progression of different chronic diseases, including cardiovascular diseases (Hegab et al., 2012; Kizer et al., 2014), diabetes mellitus (Beisswenger et al., 2013;

* Corresponding author. Department of Endocrinology, University of Picardie-Jules Verne, Amiens, France. Tel.: +33 3 22 45 59 00; fax: +33 3 22 45 53 34.
E-mail address: youssef.kouidrat@gmail.com (Y. Kouidrat).

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Table 1
Data from descriptive studies evaluating AGE metabolism in schizophrenia.

Authors	Research using controls	N	Sex (M/F)	Age (y)	Duration of illness (y)	Biomarker	Assessment method	Findings
Arai et al. (2010)	Yes	45	29/16	51.0 (±12.2)	N/A	pentosidine	HPLC assay	Elevated AGEs and concomitant low serum vitamin B6 levels, associated with genetic and functional alterations in GLO1
Miyashita et al. (2014b)	Yes	156	83/73	48.9 (±12.3)	24.1 ± 14	pentosidine	HPLC assay	Elevated AGEs and concomitant low serum vitamin B6
Katsuta et al. (2014)	Yes	137	68/69	38.9 (±13.9)	17.9 ± 14.2	pentosidine	ELISA	No significant differences between serum pentosidine levels in patients and healthy controls
Kouidrat et al. (2013)	Yes	55	34/21	43 (±11)	16.45 ± 7.83	skin AGEs	Noninvasive skin autofluorescence	Increased skin AGE compared with controls
Steiner et al. (2009)	Yes	26	17/9	34.7 (±11.3)	8 ± 9	sRAGE	ELISA	sRAGE levels increased in schizophrenia patients after 6 weeks of treatment *vs.* T0
Emanuele et al. (2011)	Yes	39	18/21	42.5 (±11.1)	NA	sRAGE	ELISA	Lower concentrations compared with controls

Jack and Wright, 2012), chronic renal failure (Arsov et al., 2014), and neurodegenerative diseases (Angeloni et al., 2014; Li et al., 2012) as well as psychiatric disorders, particularly schizophrenia (Arai et al., 2010; Kouidrat et al., 2013). There is currently a wide interest in studying the role of AGEs in different aspects of this disorder.

2. Method

This systematic review was prepared according to PRISMA guidelines (Moher et al., 2009). To identify studies eligible for this work, we conducted a literature search using the main scientific databases Embase, Pubmed, and Scopus up until July 2014. Search terms included the following keywords grouped in various combinations: « schizophrenia, advanced glycation end products, AGEs, and sRAGE ». We also examined the reference sections from the selected papers to identify any additional relevant studies. Studies were eligible for inclusion in the systematic review if (a) they were published in an English-language peer-reviewed journal; (b) the study enrolled patients with schizophrenia or schizoaffective disorders; and (c) the diagnosis was made according to Diagnostic and Statistical Manual (DSM) or International Classification of Diseases (ICD) criteria. Article titles and the abstracts of studies identified from the searches were screened and excluded from the systematic review for the following reasons: not written in English; review article, opinion, or hypothesis article. Then, after the exclusion of irrelevant abstracts, the full text of all remaining articles were critically inspected and reviewed by 2 authors (YK and AA). If required, the authors were contacted directly for additional information.

3. Results

3.1. Study characteristics

The electronic database searches identified 15 records. From these, 6 articles met all our criteria and were included in the systematic review. We clustered the retained papers into two main themes: AGEs and the pathophysiology of schizophrenia, and AGEs and cardiovascular risk in schizophrenia.

3.2. AGEs and the pathophysiology of schizophrenia

Summary data on AGE metabolism biomarkers in schizophrenia are presented in Table 1.

The relationship between oxidative stress and the etiology of schizophrenia may arise from the fact that the nervous system is particularly vulnerable to oxidative damage due to the high utilization of oxygen resulting in the production of free radicals. Several hypotheses have been postulated, including activated microglia (Ponath et al., 2007) and the failure of the antioxidant defense system (metabolic pathways that detoxify AGEs and ROS), which includes various antioxidant enzymes such as superoxide dismutase, glutathione peroxidase and the glyoxalase detoxification system (Ciobica et al., 2011; Saruwatari et al., 2013; Wu et al., 2013; Yao et al., 1998, 2006). Thus, several studies identified abnormal AGE accumulation in patients with schizophrenia by different methods (Arai et al., 2010; Steiner et al., 2009).

In a separate study, Arai et al. found that schizophrenia patients ($n = 45$) presented increased AGE accumulation that was 1.7-fold higher than in control subjects (pentosidine levels were determined by high-performance liquid chromatography). Moreover, the authors focused on vitamin B6 compounds (pyridoxal, pyridoxine), which function as antioxidants and thus offer protection against oxidative stress under various pathophysiological and or experimental conditions. Therefore, the depletion of the vitamin B6 tissue concentration might reflect elevated oxidative stress. Indeed, compared to healthy control subjects, a marked decrease of plasma vitamin B6 concentration was detected in schizophrenia patients (Arai et al., 2010). These findings suggest enhanced oxidative stress and two markers, pentosidine and vitamin B6, as a disease feature in a subpopulation of schizophrenia patients.

In a recent publication, the same team (Miyashita et al., 2014b) increased the sample size and validated the association of enhanced oxidative stress with schizophrenia (Miyashita et al., 2014b). They recruited 156 outpatients using DSM-IV criteria for schizophrenia or schizoaffective disorder, and 221 age-matched healthy control subjects. Plasma pentosidine concentrations in patients and healthy control subjects were 67.7 ng/mL and 41.9 ng/mL, respectively. The mean pentosidine level from schizophrenia patients was 1.6-fold higher than that of healthy control subjects. Conversely, the mean pyridoxal value was significantly reduced in schizophrenia patients compared with controls. These results are consistent with the previous report of Arai et al. (2010) and replicated the finding of idiopathic oxidative stress in a subpopulation of patients with schizophrenia (Arai et al., 2010).

In parallel, Miyashita et al. focused on the clinical features of schizophrenia observed during enhanced oxidative stress. They showed that schizophrenia patients with accumulated pentosidine

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