Aging and Disease
www.aginganddisease.org
Volume 5, Number 4; 256-262, August 2014
http://dx.doi.org/10.14336/AD.2014.0500256

Review Article

Accelerated Aging in Schizophrenia Patients: The Potential Role of Oxidative Stress

Olaoluwa O Okusaga*

Department of Psychiatry and Behavioral Sciences, the University of Texas Health Science Center at Houston, Texas, USA

[Received November 14, 2013; Revised November 30, 2013; Accepted December 3, 2013]

ABSTRACT: Several lines of evidence suggest that schizophrenia, a severe mental illness characterized by delusions, hallucinations and thought disorder is associated with accelerated aging. The free radical (oxidative stress) theory of aging assumes that aging occurs as a result of damage to cell constituents and connective tissues by free radicals arising from oxygen-associated reactions. Schizophrenia has been associated with oxidative stress and chronic inflammation, both of which also appear to reciprocally induce each other in a positive feedback manner. The buildup of damaged macromolecules due to increased oxidative stress and failure of protein repair and maintenance systems is an indicator of aging both at the cellular and organismal level. When compared with age-matched healthy controls, schizophrenia patients have higher levels of markers of oxidative cellular damage such as protein carbonyls, products of lipid peroxidation and DNA hydroxylation. Potential confounders such as antipsychotic medication, smoking, socio-economic status and unhealthy lifestyle make it impossible to solely attribute the earlier onset of aging-related changes or oxidative stress to having a diagnosis of schizophrenia. Regardless of whether oxidative stress can be attributed solely to a diagnosis of schizophrenia or whether it is due to other factors associated with schizophrenia, the available evidence is in support of increased oxidative stress-induced cellular damage of macromolecules which may play a role in the phenomenon of accelerated aging presumed to be associated with schizophrenia.

Key words: Schizophrenia, accelerated aging, oxidative stress, free radicals, inflammation

There are multiple definitions of aging and disagreement exists within the field about what aging really is and is not [1]. Nevertheless, a conceptually useful and operational definition of aging is: a decline in intrinsic physiological function which is age-dependent or age-progressive and leads to an increase in age-specific mortality rate (i.e., a reduction in survival rate) and a decrease in age-specific reproductive rate [2, 3]. Schizophrenia, a severe mental illness characterized by delusions, hallucinations and thought disorder has been proposed to be associated with accelerated aging [4, 5], implying that whole-body aging-related physiological and structural changes appear at an earlier age in schizophrenia patients compared with the general population.

Knowledge of the aging process is still evolving and current biological theories of aging can be divided into two broad categories namely, programmed and error/damage theories [6]. The programmed theories assume that aging follows a biological timetable or internal biological clock which regulates aging via changes in the expression of genes involved in maintenance, repair and defense mechanisms in the body;

***Correspondence should be addressed to:** Dr Olaoluwa O. Okusaga, MD, MScPHR, University of Texas Harris County Psychiatric Center, Houston, Texas, 77021, USA. Email: Olaoluwa.O.Okusaga@uth.tmc.edu

ISSN: 2152-5250

the error/damage theories imply that internal and external assaults result in damage to the organism at multiple levels [6]. The two main biological theories involve several mechanisms including genetic, immunologic, endocrine and redox mechanisms. Assuming that the hypothesis of accelerated aging in schizophrenia is valid, one would expect that the several mechanisms subsumed under the two main biological theories of aging would be operative in schizophrenia patients at a higher rate than the general population. Schizophrenia has been associated with oxidative stress [7] and oxidative stress has in turn been implicated in the aging process [8]. Consequently, this review will specifically focus on the free radical (oxidative stress) theory of aging and its relevance to the hypothesis of accelerated aging in schizophrenia. Lines of evidence in support of accelerated aging in schizophrenia will first of all be described followed by a brief review of the free radical or oxidative stress theory of aging. Oxidative stress and its consequences, the role of inflammation and suggestions for future work will be described in subsequent sections.

Accelerated aging in schizophrenia

A number of findings in the schizophrenia literature support the hypothesis of accelerated aging in the disorder. One such finding is the 10-25-year reduction in life expectancy (three-fold higher mortality rates) in schizophrenia patients when compared with the general population [9]. In addition, the median age of admission to nursing homes is 15 years earlier in schizophrenia patients relative to the general population (i.e. 65 years vs. 80 years), and the risk of admission to nursing homes is almost 4 times higher in middle-aged (40-64 years old) schizophrenia patients compared to individuals of the same age in the general population [10]. Across the lifespan, schizophrenia patients perform worse on tests of cognition when compared to healthy controls but schizophrenia patients also begin to exhibit decline in aging-sensitive cognitive domains at an earlier age. For example, the performance of schizophrenia patients aged 40-49 years on cognitive tests of working and episodic memory and psychomotor speed (domains most sensitive to aging) was inferior to that of healthy subjects 70 years and older [11]. There is also evidence to suggest an accelerated rate of aging-related brain volume reduction in patients with schizophrenia compared to healthy controls [12, 13].

Metabolic abnormalities that are associated with aging, such as elevated pulse pressure (the difference between systolic and diastolic blood pressure), diabetes, low testosterone and low bone mass, are more prevalent in schizophrenia patients compared to age-matched controls [4, 14, 15, 16, 17] and these findings provide additional support for accelerated aging in schizophrenia. Reduced telomere length (an indicator of aging) has also been found to be more prevalent in schizophrenia patients relative to matched controls [18] and some authors have proposed that schizophrenia is a form of progeria i.e. syndrome of premature aging [5]. It is however important to mention that several schizophrenia-associated factors such as antipsychotic medication, smoking, poor medical care and other unhealthy habits may contribute to the above findings in schizophrenia. Nevertheless, on the basis that schizophrenia has been associated with diabetes since the nineteenth century, i.e. prior to the introduction of antipsychotics [19] and low testosterone was found in newly diagnosed antipsychotic-naïve patients [15], medication effects alone might not account for all aging-related findings.

Free Radical (Oxidative Stress) Theory of Aging

Over 50 years ago, Harman proposed the landmark free radical theory of aging in which he posited that aging occurs as a result of damage to cell constituents and connective tissues by free radicals arising from molecular oxygen-associated reactions catalyzed by oxidative enzymes in cells and traces of metals such as cobalt, manganese and iron in tissues [20]. A free radical is any species that contains an unpaired electron [21] and examples include hydroxyl radical ($OH^{\bullet}$), superoxide ($O_2^{\bullet -}$), and nitric oxide ($NO^{\bullet}$). Other oxidants such as hydrogen peroxide (H_2O_2), peroxynitrite ($ONOO^-$), and Hypochlorous acid (HOCl) do not contain unpaired electrons and therefore do not qualify as free radicals. Reactive oxygen species (ROS) and reactive nitrogen species (RNS) are terms now used to collectively describe free radicals and other oxidants such as H_2O_2, HOCl, $ONOO^-$ [21, 22]. Over a decade after his original proposal, Harman's free radical theory was further strengthened by the discovery of superoxide dismutase (SOD) in 1969, and the recognition that SOD was an antioxidant enzyme produced in the body led to the hypothesis that it evolved to counter the deleterious effects of free radical accumulation [23]. Apart from SOD, other important antioxidant enzymes include catalase and glutathione peroxidase. The term oxidative stress is used to describe a state of imbalance between prooxidant ROS/RNS and antioxidant levels in favor of prooxidants in cells and tissues [24].

ROS/RNS can damage cell constituents such as lipids, proteins and DNA, and the accumulated damage may contribute to the process of cell senescence (growth arrest and loss of the capacity to replicate) [8]. Cellular senescence has been causally implicated in the development of age-related phenotypes and the removal of senescent cells can potentially prevent or slow down

tissue dysfunction and prolong health span [25]. ROS/RNS may damage cellular constituents by: (1) reacting with DNA bases or with deoxyribose as in the joining of $OH^{\bullet}$ radical to the C-8 position of guanine to form 8–hydroxyguanine [24]; (2) they can modify protein, resulting in the formation of carbonyls (the most widely studied damaging effect of ROS/RNS on proteins), dityrosine, nitrated and chlorinated tyrosines [26]; (3) they can make lipids undergo peroxidation with the formation of thiobarbituric acid reactive substances (TBARS) and malondialdehyde (MDA) [24]. In relation to protein oxidation, cysteine residues are the prime targets of many ROS and this is because many cysteine residues have a low pK_a, and are referred to as "redox-active cysteine residues," [27]. ROS-induced oxidation of protein cysteine residues involves several biochemical mechanisms including: (1) S-glutathionylation, the formation of mixed disulfides between glutathione and cysteine residues in proteins [28]; (2) S-nitrosylation, the addition or transfer of a nitroso group (NO) to cysteine [29, 30]; (3) formation of disulfide bonds [31]; (4) formation of sulfenic acid, sulfinic acid and sulfonic acid derivatives respectively [32]. Most of the oxidized forms of the cysteine residues are reversible; sulfinic acid and sulfonic were together considered irreversible but recently, enzymatic reduction of sulfinic acid has been found to be possible therefore leaving sulfonic acid as the only irreversible form [32]. Severe oxidative stress is accompanied by overoxidized forms of cysteine such as sulfinic and sulfonic acid which are dysfunctional [31, 32].

Although some have recently questioned the validity of the free radical (oxidative stress) theory of aging [33, 34], the available data suggest that it is still a viable theory which should be viewed as part of the general theory of aging [35, 36]. In addition, the original view of Harman was probably too simplistic in that ROS/RNS may not just function stochastically (as assumed by Harman) but there is now evidence indicating that ROS/RNS also function as specific signaling molecules under both physiological and pathophysiological conditions and increased protein oxidative damage during the aging process maybe a targeted rather than a stochastic phenomenon [8, 35, 37]

Oxidative stress in schizophrenia

Elevated levels of markers of oxidative stress have been reported in schizophrenia patients relative to healthy controls, and this finding cuts across several cell, tissue or body fluid types; peripheral blood [38] red blood cells [39] platelets [40] neutrophils [41] CSF [42] and brain tissue [43] of schizophrenia patients have all been documented to have abnormal oxidative stress parameters. Evidence from genetic association and gene expression studies also suggest that schizophrenia patients may have a reduced ability to mount an adequate antioxidant defense mechanism [44]. The view that schizophrenia patients may have a deficient antioxidant defense mechanism informed the clinical trials of antioxidants in this patient population. A clinical trial of adjunctive N-acetylcysteine (an antioxidant which increases the production of glutathione) showed that N-acetylcysteine significantly reduced the severity of symptoms of schizophrenia [45]. Omega-3-fatty acids are rich in eicosapentaenoic acid (shown to have antioxidant properties [46]) and adjunctive omega-3-fatty acids significantly reduced symptoms of schizophrenia in four of seven randomized controlled clinical trials [47]. Reduced antioxidant status in schizophrenia maybe independent of antipsychotic medication as a recently published meta-analysis indicated that first episode antipsychotic medication-naïve patients had reduced RBC catalase and SOD as well as reduced plasma and serum total antioxidant status compared to healthy controls [7].

Positive feedback and reciprocal induction between inflammation and oxidative stress in schizophrenia

Immune abnormality with associated inflammation has been associated with schizophrenia and results of a meta-analysis indicated that levels of pro-inflammatory cytokines such as interleukin-1-beta (IL-1β), interferon gamma (INF-γ) and tumor necrosis factor-alpha (TNF-α) are elevated in schizophrenia patients relative to controls [48]. A recent meta-analysis also found increased levels of immune cells (CD3 and CD4 lymphocytes) in medication-naïve first episode psychosis patients in comparison to healthy controls [49] suggesting that the findings might be independent of antipsychotic medication effect. In schizophrenia patients, inflammation and oxidative stress may reciprocally induce each other in a positive feedback manner [50]. Via the activation of estrogen-related receptor alpha (ERRα) and coactivator peroxisome proliferator-activated receptor gamma coactivator-1 beta (PGC1β), INF-γ can upregulate the expression of many nuclear genes encoding mitochondrial electron transport chain and induce mitochondrial ROS [51] in macrophages and this may potentially enhance oxidative stress. TNF-α has also been shown to increase mitochondrial ROS production [52]. ROS can in turn induce an inflammatory response via inflammasome (inflammasomes are intracellular multiprotein complexes triggered by exposure to infectious and endogenous danger signals of cell injury [53]) activation [54] which subsequently stimulates production of the pro-inflammatory cytokines IL-1β and IL-18 respectively [55]. Another mechanism by which ROS may induce inflammation is via the stimulation of

transcription factors such as NF-κB and activator protein-1 (AP-1), the downstream effects of which include the synthesis of proinflammatory cytokines [56] and this may maintain the cycle of induction between inflammation and oxidative stress. ROS may also enhance inflammation via the activation of stress-activated kinases such as ERK, JNK, and p38 [57]. Figure 1 depicts the possible mechanisms of reciprocal induction and positive feedback between inflammation and oxidative stress and the resulting cellular damage.

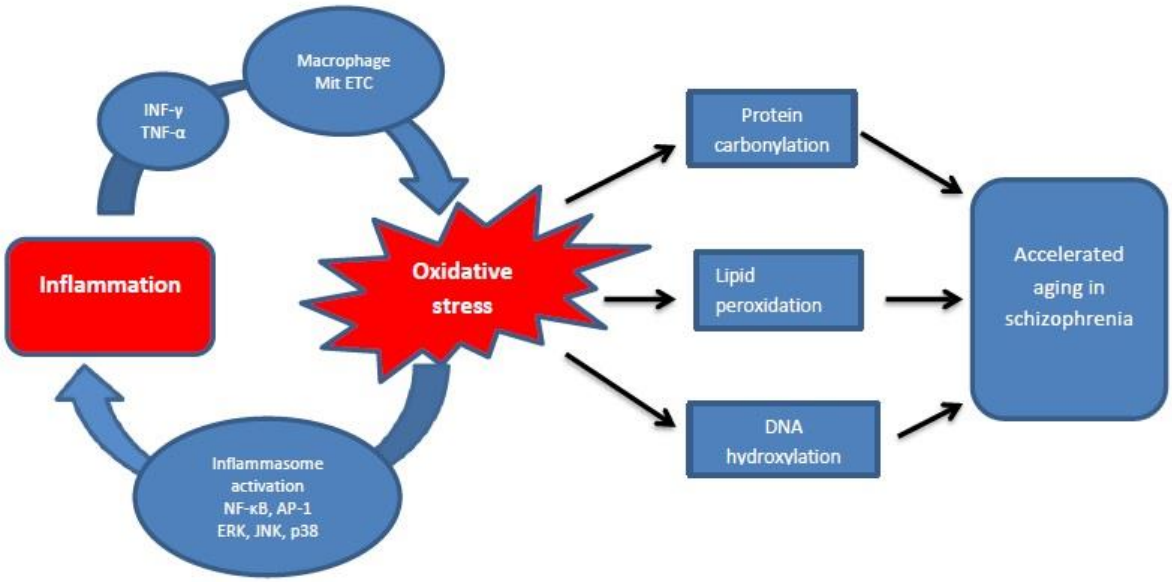

Figure 1: Inflammation and oxidative stress may reciprocally induce each other via a positive feedback loop [50]. The feedback loop involves the induction of increased production of ROS by proinflammatory cytokines (INF-γ and TNF-α) in macrophages/microglia [51] and ROS in turn enhance inflammation by activating inflammasomes, stimulating NF-κB and AP-1 as well as activating stress-activated kinases such as ERK, JNK, and p38 [55, 56]. Oxidative stress will then cause damage to cellular macromolecules including proteins, lipids and DNA leading to cell senescence which has causally been implicated in the development of age-related phenotypes. INF-γ = interferon gamma; TNF-α = tumor necrosis factor alpha; NF-κB = nuclear factor kappa B; AP-1 = activator protein 1; ERK = extracellular-signal-regulated kinase; JNK = c-Jun N-terminal kinases; Mit ETC = mitochondrial electron transport chain.

Evidence of increased oxidative damage of cellular macromolecules in schizophrenia

The buildup of damaged macromolecules due to increased oxidative stress and failure of protein repair and maintenance systems is an indicator of aging both at the cellular and organismal level [58]. Carbonyl proteins, thiobarbituric acid reactive substances (TBARS), malondialdehyde (MDA) and products of DNA oxidation are some of the altered molecules known to accumulate in aging cells [59, 60]. Based on the hypothesis of accelerated aging in schizophrenia, one would expect the rate of accumulation of damaged macromolecules to be significantly higher in schizophrenia patients relative to the general population; the results of several studies are consistent with this expectation. Dietrich-Muszalska and Olas [40] compared the concentration of carbonyl proteins (marker of irreversible and irreparable protein oxidation) in platelets from schizophrenia patients and healthy controls (patients and controls were of similar age group) and found the concentration in schizophrenia patients to be approximately 260% higher than healthy controls.

Platelets from schizophrenia patients were also found to have a significantly higher concentration of TBARS (marker of lipid peroxidation) when compared with platelets from healthy controls [61]. Herken et al [33] also found TBARS in erythrocytes to be significantly elevated in schizophrenia patients when compared to age and sex-matched healthy subjects. Urinary excretion of 8-oxo-7,8-dihydro-2′-deoxyguanosine (8-oxodG) and 8-oxo-7,8-dihydroguanosine(8-oxoGuo) are biomarkers of systemic oxidative damage of DNA and RNA, and a recent study reported the median urinary excretion of both 8-oxodG and 8-oxoGuo to be approximately 20% higher in the schizophrenia patients relative to age- and sex-matched healthy controls [62]. The higher rate of urinary excretion of the two markers of oxidative DNA and RNA damage in schizophrenia patients persisted after controlling for demographic and lifestyle factors potentially associated with oxidative stress such as smoking, alcohol intake, exercise and oral contraceptive use as well as clinical and metabolic factors found to be different between the two groups (waist–hip ratio, pulse, triglycerides, HbA1c, CRP, TSH and cortisol).

Conclusion

Aging-related metabolic, physical, and cognitive changes appear at an earlier age in schizophrenia when compared to the general population. The currently available data however preclude the unequivocal ascription of the premature appearance of aging-related changes solely to having a diagnosis of schizophrenia because the effect of potential confounders (e.g. antipsychotic medication, smoking, socio-economic status and unhealthy lifestyle) cannot be completely ruled out. Also, the increased oxidative stress in schizophrenia cannot be conclusively attributed to the diagnosis alone as the effects of factors potentially associated with oxidative stress (in particular smoking, diet and antipsychotic medication) may be significant. Regardless of whether oxidative stress can be attributed solely to a diagnosis of schizophrenia or whether it is due to other factors associated with schizophrenia, the evidence is in support of increased oxidative stress-induced cellular damage of macromolecules which may play a role in accelerated aging presumed to be associated with schizophrenia. If the phenomenon of accelerated aging is consistently replicated and validated in large, well-designed prospective studies, more in-depth study of this phenomenon could enhance our understanding of the aging process especially in light of the free radical (oxidative stress) theory of aging. Future work should include evaluation and comparison of the impact of new generation (atypical) and older generation (typical) antipsychotics on aging-related changes and markers of oxidative stress damage in patients with schizophrenia. Evaluation of the effect of adjunctive use of antioxidant medications on aging-related changes in schizophrenia is also likely to be informative and may help consolidate current knowledge of the aging process.

References

[1] de Grey AD (2013). The desperate need for a biomedically useful definition of "aging". Rejuvenation Res,16: 89-90.

[2] Flatt T (20120. A new definition of aging? Front Genet, 3: 148.

[3] Rose MR. Evolutionary Biology of Aging. Oxford: Oxford University Press; 1991.

[4] Kirkpatrick B, Messias E, Harvey PD, Fernandez-Egea E, Bowie CR (2008). Is Schizophrenia a Syndrome of Accelerated Aging? Schizophr Bull, 34: 1024–1032.

[5] Papanastasiou E, Gaughran F, Smith S (2011). Schizophrenia as segmental progeria. J R Soc Med, 104: 475-484.

[6] Jin K (2010). Modern Biological Theories of Aging. Aging Dis, 1: 72-74.

[7] Flatow J, Buckley P, Miller BJ (2013). Meta-analysis of oxidative stress in schizophrenia. Biol Psychiatry, 74: 400-409.

[8] Finkel T, Holbrook NJ (2000). Oxidants, oxidative stress and the biology of ageing. Nature, 408: 239–247.

[9] Laursen TM, Munk-Olsen T, Vestergaard M (2012). Life expectancy and cardiovascular mortality in persons with schizophrenia. Curr Opin Psychiatry, 25: 83-88.

[10] Andrews AO, Bartels SJ, Xie H, Peacock WJ (2009). Increased risk of nursing home admission among middle aged and older adults with schizophrenia. Am J Geriatr Psychiatry, 17: 697-705

[11] Loewenstein DA, Czaja SJ, Bowie CR, Harvey PD (2012). Age-associated differences in cognitive performance in older patients with schizophrenia: a comparison with healthy older adults. Am J Geriatr Psychiatry, 20: 29-40.

[12] Kochunov P, Glahn DC, Rowland LM, Olvera RL, Winkler A, Yang YH et al (2013). Testing the hypothesis of accelerated cerebral white matter aging in schizophrenia and major depression. Biol Psychiatry, 73: 482-491.

[13] Cobia DJ, Smith MJ, Wang L, Csernansky JG (2012). Longitudinal progression of frontal and temporal lobe changes in schizophrenia. Schizophr Res, 139: 1-6.

[14] Papanastasiou E (2013). The prevalence and mechanisms of metabolic syndrome in schizophrenia: a review. Ther Adv Psychopharmacol, 3: 33-51.

[15] Fernandez-Egea E, Garc á-Rizo C, Miller B, Parellada E, Justicia A, Bernardo M, et al (2011). Testosterone in newly diagnosed, antipsychotic-naive men with nonaffective psychosis: a test of the accelerated aging hypothesis. Psychosom Med, 73: 643-647.

[16] Renn JH, Yang NP, Chueh CM, Lin CY, Lan TH, Chou P. Bone mass in schizophrenia and normal populations

across different decades of life. BMC Musculoskelet Disord, 10:1.
[17] Sugawara N, Yasui-Furukori N, Umeda T, Tsuchimine S, Fujii A, Sato Y, et al (2012). Effect of age and disease on bone mass in Japanese patients with schizophrenia. Ann Gen Psychiatry, 11:5.
[18] Fernandez-Egea E, Bernardo M, Heaphy CM, Griffith JK, Parellada E, Esmatjes E, et al (2009). Telomere length and pulse pressure in newly diagnosed, antipsychotic-naive patients with nonaffective psychosis. Schizophr Bull, 35: 437-442.
[19] Maudsley H. The Pathology of Mind. 3rd ed. London: Macmillan;1979.
[20] Harman D (19566). Aging: a theory based on free radical and radiation chemistry. J Gerontol, 11: 298–300.
[21] Halliwell B (1989). Tell me about free radicals, doctor: a review. J R Soc Med, 82: 747–752.
[22] Martínez MC, Andriantsitohaina R (2009). Reactive nitrogen species: molecular mechanisms and potential significance in health and disease. Antioxid Redox Signal, 11: 669-702.
[23] McCord JM, Fridovich I (1969). Superoxide dismutase. An enzymic function for erythrocuprein (hemocuprein). J Biol Chem, 244: 6049–6055.
[24] Kalyanaraman B (2013). Teaching the basics of redox biology to medical and graduate students: Oxidants, antioxidants and disease mechanisms. Redox Biol, 1: 244-257.
[25] Baker DJ, Wijshake T, Tchkonia T, LeBrasseur NK, Childs BG, van de Sluis B, et al (2012). Clearance of p16Ink4a-positive senescent cells delays ageing-associated disorders. Nature, 479: 232–236.
[26] Ahmed EK, Rogowska-Wrzesinska A, Roepstorff P, Bulteau AL, Friguet B (2010). Protein modification and replicative senescence of WI-38 human embryonic fibroblasts. Aging Cell, 9: 252–272.
[27] Jeong J, Jung Y, Na S, Jeong J, Lee E, Kim MS, et al (2011). Novel oxidative modifications in redox-active cysteine residues. Mol Cell Proteomics, 10: M110.000513.
[28] Giustarini D, Rossi R, Milzani A, Colombo R, Dalle-Donne I (2004). S-glutathionylation: from redox regulation of protein functions to human diseases. J Cell Mol Med, 8: 201-212.
[29] Hess DT, Matsumoto A, Kim SO, Marshall HE, Stamler JS (2005). Protein S-nitrosylation: purview and parameters. Nat Rev Mol Cell Biol, 6: 150-166.
[30] Gould N, Doulias PT, Tenopoulou M, Raju K, Ischiropoulos H (2013). Regulation of protein function and signaling by reversible cysteine S-nitrosylation. J Biol Chem, 288: 26473-26479.
[31] Held JM, Gibson BW (2012). Regulatory control or oxidative damage? Proteomic approaches to interrogate the role of cysteine oxidation status in biological processes. Mol Cell Proteomics, 11: R111.013037.
[32] Charles RL, Schröder E, May G, Free P, Gaffney PR, Wait R, et al (2007). Protein sulfenation as a redox sensor: proteomics studies using a novel biotinylated dimedone analogue. Mol Cell Proteomics, 6:1473-1484.
[33] Gems D, Doonan R (2009). Antioxidant defense and aging in *C. elegans*: is the oxidative damage theory of aging wrong? Cell Cycle, 8:1681–1687.
[34] Lapointe J, Hekimi S (2010).When a theory of aging ages badly. Cell Mol Life Sci, 67: 1–8.
[35] Afanas'ev I (2010). Signaling and Damaging Functions of Free Radicals in Aging-Free Radical Theory, Hormesis, and TOR. Aging Dis, 1: 75-88.
[36] Liochev SI (2013). Reactive oxygen species and the free radical theory of aging. Free Radic Biol Med, 60: 1-4.
[37] Yan LJ, Sohal RS (1998. Mitochondrial adenine nucleotide translocase is modified oxidatively during aging. Proc Natl Acad Sci U S A, 95: 12896-12901.
[38] Korotkova EI, Misini B, Dorozhko EV, Bukkel MV, Plotnikov EV, Linert W (2011). Study of OH Radicals in Human Serum Blood of Healthy Individuals and Those with Pathological Schizophrenia. Int J Mol Sci, 12: 401-410.
[39] Herken H, Uz E, Ozyurt H, Söğüt S, Virit O, Akyol O (2001). Evidence that the activities of erythrocyte free radical scavenging enzymes and the products of lipid peroxidation are increased in different forms of schizophrenia. Mol Psychiatry, 6: 66-73.
[40] Dietrich-Muszalska A, Olas B (2009). Modifications of blood platelet proteins of patients with schizophrenia. Platelets, 20: 90-96.
[41] Sirota P, Gavrieli R, Wolach B (2003). Overproduction of neutrophil radical oxygen species correlates with negative symptoms in schizophrenic patients: Parallel studies on neutrophil chemotaxis, superoxide production and bactericidal activity. Psychiatry Res, 121:123–132.
[42] Do KQ, Trabesinger AH, Kirsten-Krüger M, Lauer CJ, Dydak U, Hell D, et al. (2000). Schizophrenia: Glutathione deficit in cerebrospinal fluid and prefrontal cortex in vivo. Eur J Neurosci, 12: 3721–3728.
[43] Yao JK, Leonard S, Reddy RD (2004). Increased nitric oxide radicals in postmortem brain from patients with schizophrenia. Schizophr Bull, 30: 923-934.
[44] Chowdari KV, Bamne MN, Nimgaonkar VL (2011). Genetic association studies of antioxidant pathway genes and schizophrenia. Antioxid Redox Signal, 15: 2037–2045.
[45] Berk M, Copolov D, Dean O, Lu K, Jeavons S, Schapkaitz I, et al. (2008). N-acetyl cysteine as a glutathione precursor for schizophrenia— a double-blind, randomized, placebo-controlled trial. Biol Psychiatry, 64: 361–368.
[46] Palaniswamy KS, Vishwanadha VP, Ramalingam Singaravelu S (2013). Fish oil rich in eicosapentaenoic acid protects against oxidative stress-related renal dysfunction induced by TCDD in Wistar rats. Cell Stress Chaperones. [Epub ahead of print].
[47] Torrey EF, Davis JM (2012). Adjunct treatments for schizophrenia and bipolar disorder: what to try when you are out of ideas. Clin Schizophr Relat Psychoses, 5: 208-216.
[48] Miller B, Buckley P, Seabolt W, Mellor A, Kirkpatrick B (2011). Metaanalysis of cytokine alterations in schizophrenia: Clinical status and antipsychotic effects. Biol Psychiatry, 70: 663–671.

[49] Miller BJ, Gassama B, Sebastian D, Buckley P, Mellor A (2013). Meta-analysis of lymphocytes in schizophrenia: clinical status and antipsychotic effects. Biol Psychiatry, 73: 993-999.

[50] Bitanihirwe BK, Woo TU (2011). Oxidative stress in schizophrenia: An integrated approach. Neurosci Biobehav Rev, 35: 878–893.

[51] Sonoda J, Laganière J, Mehl IR, Barish GD, Chong LW, Li X, et al (2007). Nuclear receptor ERR alpha and coactivator PGC-1 beta are effectors of IFN-gamma-induced host defense. Genes Dev, 21:1909-1920.

[52] Corda S, Laplace C, Vicaut E, Duranteau J (2001). Rapid reactive oxygen species production by mitochondria in endothelial cells exposed to tumor necrosis factor-alpha is mediated by ceramide. Am J Respir Cell Mol Biol, 24:762-768.

[53] Geldhoff M, Mook-Kanamori BB, Brouwer MC, Troost D, Leemans JC, Flavell RA, et al (2013). Inflammasome activation mediates inflammation and outcome in humans and mice with pneumococcal meningitis. BMC Infect Dis, 13: 358.

[54] Nathan C, Cunningham-Bussel A (2013). Beyond oxidative stress: an immunologist's guide to reactive oxygen species. Nat Rev Immunol, 13: 349-361.

[55] Latz E, Xiao TS, Stutz A (2013). Activation and regulation of the inflammasomes. Nat Rev Immunol, 13: 397-411.

[56] Reuter S, Gupta SC, Chaturvedi MM, Aggarwal BB (2010). Oxidative stress, inflammation, and cancer: how are they linked? Free Radical Biol. Med, 49: 1603–1616.

[57] Rawdin BJ, Mellon SH, Dhabhar FS, Epel ES, Puterman E, Su Y, et al (2013). Dysregulated relationship of inflammation and oxidative stress in major depression. Brain Behav Immun, 31: 143-152.

[58] Stadtman ER (2006). Protein oxidation and aging. Free Radical Research, 40:1250–1258.

[59] Rucci A, Ensinck MA, Mufarrege N, Cotorruelo C, Borrás SG, Racca L, et al (2010). Modifications of band 3 and oxidation level of membrane proteins in senescent erythrocytes. Clin Biochem, 43: 1171-1173.

[60] Muteliefu G, Shimizu H, Enomoto A, Nishijima F, Takahashi M, Niwa T (2012). Indoxyl sulfate promotes vascular smooth muscle cell senescence with upregulation of p53, p21, and prelamin A through oxidative stress. Am J Physiol Cell Physiol, 303:C126-134.

[61] Dietrich-Muszalska A, Olas B, Rabe-Jablonska J (2005). Oxidative stress in blood platelets from schizophrenic patients. Platelets, 16:386-391.

[62] Jorgensen A, Broedbaek K, Fink-Jensen A, Knorr U, Greisen Soendergaard M, Henriksen T (2013). Increased systemic oxidatively generated DNA and RNA damage in schizophrenia. Psychiatry Res, 209: 417-23.