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

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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;
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-naive 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•), superoxide (O2•-), and nitric oxide (NO•). Other oxidants such as hydrogen peroxide (H2O2), 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 H2O2, 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 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 pKₐ 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, sulfonic acid and sulfenic acid derivatives respectively [32]. Most of the oxidized forms of the cysteine residues are reversible; sulfenic acid and sulfonic were together considered irreversible but recently, enzymatic reduction of sulfenic 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 sulfenic 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.

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.

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