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Free Radicals, Oxidative stress and Antioxidant Therapeutics in Schizophrenia: An overview

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Abstract

When an overload of free radicals cannot gradually be destroyed, their accumulation in the body generates a phenomenon called oxidative stress. Oxidative stress has been suggested to contribute to the pathophysiology of schizophrenia. In particular, oxidative damage to lipids, proteins, and DNA as observed in schizophrenia. Experimental models have demonstrated that oxidative stress induces behavioral and molecular anomalies strikingly similar to those observed in schizophrenia. The body has several mechanisms to counteract oxidant stress by producing antioxidants which are either naturally produced in situ or externally supplied through foods and/ or supplements. Recently, available evidence points towards an alteration in the of antioxidant defense systems in schizophrenia. Oxidative stress has been implicated in the pathogenesis of diverse disease states, and may be a common pathogenic mechanism underlying many major psychiatric disorders, as the brain has comparatively greater vulnerability to oxidative damage. This review aims to overview the current evidence for the role of oxidative damage in schizophrenia, and its academic and clinical implications. Recent clinical studies have shown antioxidant treatment to be effective in ameliorating schizophrenic symptoms. Hence, describing antioxidant therapeutic strategies to tackle oxidative stress and the resulting physiological disturbances provide an exciting opportunity for the treatment and ultimately prevention of schizophrenia. These data suggest that oxidative mechanisms may form unifying common pathogenic pathways in schizophrenia and thus introduce new targets for the development of therapeutic interventions.

Keywords: Free radicals, Oxidative stress, Schizophrenia, Antioxidants.

Introduction

Schizophrenia is a debilitating, hereditary, disorder of the brain, resulting from abnormalities that arises early in life and disrupt normal development of the brain and has a lifetime risk of 1% and affects at all age groups (average age at the onset 24±4.6 year) in many culture around the world. The onset usually occurs around 18-25 years of age and is often preceded by pre-morbid behavioral deviations, such as social withdrawal and affective changes (1).

The theory of oxidative stress as pathological mechanisms at its most basic concept referred to as the oxygen paradox that while oxygen is essential for aerobic life, excessive amount of its free radical metabolic byproducts are toxic. This hypothesis has theoretical appeal, as the brain is considered particularly susceptible to oxidative damage for several reasons. These include, its high oxygen consumption rate (20% of the total oxygen inhaled by the body) that account for increased generation of oxygen free radicals and reactive oxygen species like superoxide radicals, singlet oxygen, hydrogen peroxide, hydroxyl radicals. Also, brain is enriched with polyunsaturated fatty acids that render them vulnerable to oxidative attack (2). The concentration of various antioxidants like Superoxide dismutase, catalase, glutathione peroxidase, glutathione reductase, reduced glutathione is low in brain. This burden is increased by a number of factors including the oxidative potential of monoamines such as the glutamate as well as the generation of secondary oxidative cellular insults through the neurotoxic effects of released excitatory amines (particularly dopamine) and secondary inflammatory responses. In addition to these factors, brain has high concentration of ascorbate and iron in certain regions which provide favorable environment for the generation of ROS and reducing the potential of neurotransmission. All these intrinsic factors together with growing evidence for neurodegenerative changes associated with many psychiatric syndromes may suggest fundamental pathological pathways and their interactions may provide a beneficial conceptual framework and subsequent means of therapeutic implication (1).

Oxidative stress and antioxidant defense system

Oxygen is an element indispensable for life. When cells use oxygen to generate energy, free radicals are created as a consequence of ATP (adenosine triphosphate) production by the mitochondria. These by products are generally reactive oxygen species (ROS) and reactive nitrogen species (RNS) that results from the cellular redox process (oxidation and reduction) (3 and 4). When produced in excess, free radicals and oxidants generate a phenomenon called oxidative stress, a deleterious process that can seriously alter the cell membranes and other structures such as proteins, lipids, lipoproteins, and deoxyribonucleic acids (DNA) (2 and 5). The brain is particularly vulnerable to oxidative damage, given its relatively low contents of antioxidants defenses in addition to its high metal content, which can catalyze the formation of ROS/RNS (6).

The potential toxicity of ROS/RNS in the brain is counteracted by a number of antioxidants that can protect the brain against oxidative damage in several ways, including: 1) removal of ROS/RNS (7), 2) inhibition of ROS/RNS formation, and 3) binding metal ions needed for catalysis of ROS/RNS generation. Superoxide dismutase, catalase, glutathione peroxidase and glutathione reductase are well known major intracellular antioxidant enzymes. Other notable defense mechanisms against free radical induced and nitrosative stress include α-tocopherol, bilirubin, albumin, uric acid, niacin, carotenoids and flavonoides. Thioredoxine and

thioredoxine reductase can catalyze the regeneration of many antioxidant molecules, including ascorbic acid, ubiquinone, lipoic acid and as such constitute an important antioxidant defense against ROS/RNS (2, 5-10).

Oxidative stress induced pathogenesis schizophrenia

Over the last decade there has been a proliferation of information on oxidative stress mechanism in the psychiatric literature. The greatest volume of oxidation biology data is present in schizophrenia. Demonstration of antioxidative effects of established therapeutic agents and clinical trials of antioxidant therapies complete the evidence base. Such manifold evidences strengthen the hypothesis, that oxidative stress is a common pathological process in major neuropsychiatric disorders. As the direct measurement of free radicals concentration is not possible because of their short half life and low concentration. Oxidative status can be estimated by assay of ROS metabolites such as Malondialdehyde, nitric oxide and antioxidant enzymes (SOD, CAT, and GPx), antioxidants like GSH, vitamin E (α –tocopherol), vitamin C (ascorbic acid), albumin, and uric acid. In the essence of these studied have demonstrated reduced concentration of antioxidants such as albumin and bilirubin in schizophrenia as well as there is GSH dysregulation and increased lipid peroxidation products (1, 2, 4, 11).

Oxidative stress caused by elevated dopamine oxidation levels may enhance striatal glutamatergic neurotransmission leading to late onset long lasting permanent CNS damage. Studies reported that nitric oxide (NO) may have a role in the pathophysiology of schizophrenia. NO is a gaseous neurotransmitter which is closely connected to dopaminergic and serotoninergic neurotransmission (12, 13). This provides a rational for the involvement of NO and its pathway in schizophrenia. Moreover by its interaction with superoxide, NO can produce peroxy nitrite. The focus of this review is on examining the evidence for oxidative stress involvement in neuropsychiatric disorders and to comment on the therapeutic and research approach of this knowledge.

Discussion

A literature search was conducted using the PsycINFO, CINAHL PLUS, BIOSIS Previews Medline, Pubmed, and Cochrane databases. Search terms entered included: ‘oxidative, oxidative stress, reactive oxygen species, reactive nitrogen species, antioxidants, lipid peroxidation, thiobarbituric acid reactive substances, DNA damage, psychiatry, pathogenesis, schizophrenia, anxiety disorder, personality disorder, autism, attention deficit hyperactivity disorder, glutathione and treatment’, grouped in various combinations. This was supplemented by a hand search of references in selected articles, as well as references obtained from researchers of oxidative mechanisms in the field of psychiatry.

NO in Schizophrenia: Clinical study evidences

NO is an important messenger molecule involved in many physiological and pathological processes within the mammalian body, both beneficial and detrimental (14, 15). Being a free radical, NO has both pro- and antioxidant properties (16). Evidence is accumulating that NO may be involved in the pathophysiology of schizophrenia given the various roles that NO plays in the brain, such as regulating synaptic plasticity, neurotransmitter release, and neurodevelopment (17- 21). Nitric oxide is especially important as the second messenger of NMDA receptor activation, which interacts with both dopaminergic and serotonergic pathways (22, 23). Abnormal functioning of these pathways has been suggested to be involved in the pathophysiology of schizophrenia. Perhaps relevant to the previous connection are the findings suggesting that nitric oxide synthase

(NOS, an enzyme widely expressed throughout the brain and which is responsible for NO production in the central nervous system) inhibitors protect against phencyclidine (PCP) induced schizophrenia-mimicing phenotypes such as PPI deficits and cognitive inflexibility in animals (24, 25, 26).

Some studies have examined peripheral concentrations of the free radicals, NO in patients with schizophrenia by measuring its metabolites, nitrites and nitrates, but have yielded inconsistent results. Whilst some have found elevated plasma NO (27, 28, 29, 30, 31, 32) and reduced polymorphonucleocyte NO in those with schizophrenia compared with controls, no significant changes were found in plasma and platelet NO (33). Comparatively lower concentrations of the NO metabolites were found in the cerebrospinal fluid (CSF) of schizophrenia patients (34) compared with control patients who presented with non-inflammatory and non-degenerative neurological conditions, but these metabolites were significantly increased in a sample of post-mortem caudate specimens (35). The disparate sample sizes, patient characteristics, tissue specimen types and substances measured in these studies, and the many inherent metabolic variables in any given individual, make direct comparison of these results difficult, although they support the presence of abnormal NO metabolism in schizophrenia. One of the recent experiments develops the method of hydroxyl (OH•) radical detection in human serum in patients with pathological schizophrenia shows increased levels of OH• radicals in patients compared to controls. Interestingly, postmortem studies have reported elevated levels of NO and NOS in brain tissue of subjects with schizophrenia and have suggested that NOS may be activated in the illness (35-38). However, the evidence surrounding NO metabolites in schizophrenia has been inconsistent with studies reporting both increased (28 and 39) and decreased (40-42) levels. A negative correlation was observed between NO metabolite levels and positive and negative syndrome scale (PANNS) scores in schizophrenia subjects, indicating that reduced plasma NO metabolites maybe related to the severity of negative symptoms in schizophrenia (42). Altered populations or distribution of NOS-containing neurons have been reported in frontal, temporal, cortices, hypothalamus and cerebellum in schizophrenia (43- 46). The cholinergic receptors known to be sensitive to NO toxicity were decreased in both blood and cortex of patients with schizophrenia (47 and 48). Patients with schizophrenia frequently smoke cigarettes and often smoke heavier than the normal population (49-51). A series of studies in humans has implicated the α7 nicotinic acetylcholine receptor in the physiology of P50 auditory gating (a measure of pre-attentive auditory processing). Nicotine gum and physostigmine were found to improve gating in the relatives of persons with schizophrenia who also had impaired auditory gating (52). Thus, NO appears to influence neurotransmission (e.g. cholinergic transmission) and may play a role in some of the endophenotypes associated with schizophrenia.

Homocysteine in Schizophrenia

Homocysteine (Hcy) is the demethylated derivative of methionine, which, after conversion to s-adenosyl methionine, is the most important methyl group donor in the body. Hcy is a neuro and vasculo-toxic intermediary product and can be trans-sulfurated to cystathione and subsequently to cysteine which is a component of glutathione (52). Hcy was demonstrated to act as an agonist at the glutamate binding site of the N-methyl-D-aspartate (NMDA) receptor, causing cytoplasmic calcium influx, decreased cellular viability and increased reactive

oxygen species within cells. These experiments also showed that glycine potentiates the neurotoxic effect. Neurotoxicity mediated by activation of the NMDA receptor is dependent upon compromise of cellular energy production. Studies with cultured cerebellar granular cells concluded that activation of the NMDA receptor by Hcy leads to neurotoxicity from free radical formation. Hcy has also been suggested as useful biomarker of oxidative stress in variety of Hcy arises from generation of ROS during its catabolism, which could oxidize membrane lipids and proteins, including enzymes. In fact, it has been suggested that Hcy may have a significant influence on the development and clinical symptoms of schizophrenia. Hcy increases apoptosis in cultured human leukemic cells exposed to 3- deaza adenosine. The apoptotic damage to DNA caused by Hcy-thiolactone in cultured human leukemic cell is mediated by increased hydrogen peroxide production and caspase activation in cultured rat hippocampal neurons (52, 53). The current view of the origin of oxidative stress in cells exposed to increased levels of Hcy is that auto-oxidation of thiol groups generates hydrogen peroxide and the ROS, superoxide, hydroxyl radicals leading to oxidant stress. Recent reviews have summarized the extensive literature on vascular oxidative stress in hyperhomocysteinemia and the key role of GPx in modifying endothelial dysfunction from oxidant stress (54 and 55).

Hcy enhances superoxide anion release and NADPH oxidase assembly by human neutrophils. In addition to this Hcy increases the production of hydrogen peroxide and stimulates migration of neutrophils either in suspension or adherent to fibrin. A recent study reported that higher maternal Hcy levels may be a risk factor for schizophrenia (56). Specifically, mothers that have elevated third-trimester Hcy levels may elevate schizophrenia risk through developmental effects on brain structure and function and/or through subtle damage to the placental vasculature that compromises oxygen delivery to the fetus (56). In this context, it has been shown that high levels of Hcy are negatively correlated with glutathione peroxidase activity (57), suggesting that high levels of Hcy may also be associated with oxidative stress in schizophrenia. Altered gene expression has been shown to be associated with the pathogenesis of schizophrenia. Oxidative damage to specific gene promoters results in gene silencing. The mechanism of silencing is likely epigenetic; specifically, it may be mediated through dysregulation of DNA methylation. High Hcy levels have been shown to be accompanied by high *S*-adenosyl-Hcy levels with the elevation of *S*-adenosyl-Hcy suggested being associated with DNA hypomethylation and alterations in gene expression (58 and 59). *S*-Adenosyl-Hcy and its analogs have been reported to be a non-competitive inhibitor of catechol-*O*-methyltransferase (COMT), an enzyme that catalyze the first step in the degradation of monoamine neurotransmitters such as dopamine, epinephrine and nor-epinephrine. Elevated levels of Hcy may play some aggravating role in the pathogenesis of schizophrenia through an indirect effect on COMT (60- 62). Previous studies implicated homocysteine in the production of superoxide and oxidation of LDL by cultured arterial smooth muscle cells. A requirement for transition metal cations including ferric and cupric ions is implicated in the oxidative modification of LDL by homocysteine. In addition, Hcy react with NO to form S-nitroso-Hcy counteracting the adverse vascular effects of Hcy including endothelial dysfunction, vasoconstriction and platelet aggregation. Also Hcy decreases NO production by decreasing transcription of the mRNA for GPx in the aortic endothelial cells. These

suggest that increased Hcy induced oxidative stress promotes impaired endothelium- dependent vasodilatation presumably by decreased bioavailability of NO (12). The possible effect of homocysteine on the thioretinaco ozonide to enhance oxygen radical production needs further investigation. One possibility is that Hcy leads to increased formation of Hcy-thiolactone which displaces thioretinamide, from binding to cobalamin, forming thioco, a complex that inhibits oxidative phosphorylation and leads to accumulation of oxygen radicals and oxidative stress. Neuropsychiatrists must consider the relationship of homocysteine levels and documented usefulness of homocysteine measurements as sensitive indicator in neuropsychiatric disorders. Finally, on the basis of various observations, it proposed that antioxidants can inhibit the oxidative stress induced by homocysteine (53 and 63).

Lipid peroxidation products and antioxidants in Schizophrenia

Most data demonstrating oxidative disturbances have examined indirect measures of oxidative status, such as peripheral and brain levels of antioxidants, oxidative enzymes and products. The direct measurement of free radicals is hindered by their short half-lives and low titres. Estimating levels of oxidative reactive products provide another useful strategy to determine the impact of oxidative stress. Published studies have predominantly examined products of lipid peroxidation and DNA oxidation as markers of oxidative damage. A widely used method of measuring lipid peroxidation is the performance of thiobarbituric acid reactive substances (TBARS) assays. TBARS are low molecular- weight substances, consisting largely of malondialdehyde (MDA), which are formed from the decomposition of unstable lipid peroxidation products and react with thiobarbituric acid to form fluorescent adducts (64). TBARS have been reported to be elevated in the plasma (27, 65-7), erythrocytes, leucocytes and platelets (33, 38, 72-74) of schizophrenia patients, with abnormalities in antioxidant levels, and depleted essential polyunsaturated fatty acids, which are specially prone to lipid peroxidation (75 and 76). Data on CSF levels of TBARS in schizophrenia are limited, unexpected finding raises questions about the origins of the elevated blood TBARS that has been broadly reported in the literature, although the CSF results may have been confounded by diminished neuronal membrane substrates in the patient cohort (77) and this needs further study. A marked increase of urinary 8-isoprostaglandin F2a has recently been reported in a sample of schizophrenia patients compared with healthy controls (69). A smaller collection of studies has been published in relation to markers of DNA damage in schizophrenia. A post-mortem study examining the hippocampi of patients with ‘poor outcome’ schizophrenia and non-psychiatric controls, found a ten-fold higher presence of neuronal 8-hydroxy-2’-deoxyguanosine (8-OhdG) among the patients compared with controls, which correlated with elevated quantities of a cell-cycle activation marker (Ki-67) (78). One study reported a trend increase in lymphocyte DNA damage in schizophrenia patients compared with control subjects (79), but another found no difference, although those with schizophrenia showed a non-significant increase in sensitivity to externally induced DNA damage and decrease in DNA repair efficiency (80).

Similarly, studies involving blood assays of intrinsic antioxidants have collectively demonstrated significantly altered antioxidant activities. Reduced levels of the major antioxidant enzymes, superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GSH-Px), in

patients with schizophrenia (31, 67 and 81). Others have reported unchanged levels for these three enzymes (33), or altered concentrations of individual enzymes (27, 38, 66, 72, 74, 82-86) schizophrenic patients, other studies have reported either no change (33). Interestingly, the levels of superoxide dismutase have been found to be high in chronic schizophrenic patients (87-90) or to be low in neuroleptic-naïve first episode schizophrenic patients (86), suggesting that the efficacy of neuroleptics may in part be mediated by promoting an endogenous antioxidative mechanism (91). Another post-mortem study examined a number of cortical and subcortical areas from donors with schizophrenia and controls, and found elevated levels of two SOD isoenzymes in the frontal cortex and substantia innominata of those with schizophrenia, thereby suggesting neuroanatomical specificity of redox disturbances in schizophrenia (92). A strong negative correlation between blood GSH-Px and structural measures of brain atrophy was also reported by an early study (93). Furthermore, some studies have differentiated enzymatic changes among the schizophrenia subtypes (38 and 68), and one study showed a linear correlation between antioxidant enzyme levels and positive symptom severity (31). But, the study of Zhang et al showed that the activities of glutathione peroxidase and catalase were not affected in patients with schizophrenia (94). . In one study erythrocytes glutathione transferase (GST) activity was significantly increased and glucose 6- phosphate dehydrogenase and ceruloplasmin ferroxidase activities are decreased (73). Further supportive evidence is provided by a study reporting a 27%reduction in the CSF glutathione level in neuroleptic-naive patients with schizophrenia compared with controls, which coexisted with a 52% glutathione reduction in the medial prefrontal cortex, as measured by magnetic resonance spectroscopy (95).

The antioxidants uric acid (88), albumin and bilirubin (96), and the plasma total antioxidant status (TAS) (71 and 88,) have also been reported to be lower in patients with schizophrenia. Other study found no impairment of antioxidative defense as determined using the same indices, in those with first-episode affective psychosis (97), suggesting that oxidative stress may be involved at different stages in the two groups of disorders.

In tandem with the peripheral antioxidant abnormalities found in patients with schizophrenia, post-mortem brain tissue studies have reported significantly lower levels of glutathione in both its reduced (GSH) and oxidized forms (GSSG), and the two enzymes responsible for conversions between these two forms (GSH-Px, and glutathione reductase or GR), in the caudate region from donors with schizophrenia compared with those with other psychiatric conditions and without psychiatric conditions. Deficiency of glutathione, the major intracellular antioxidant, in its reduced form (GSH), has been observed and suggested to be of pathophysiological significance in schizophrenia (72 and 86). In addition, magnetic resonance spectroscopy studies have shown that levels of GSH were reduced by 52% in the prefrontal cortex and by 27% in cerebrospinal fluid of drug-naïve schizophrenia patients (95). However, other spectroscopy studies have failed to detect a decrease in the levels of GSH in the anterior cingulated cortex, posterior medial frontal cortex or the medial temporal lobe (98-100).

Therapeutic implications

Pharmacological treatments for millions worldwide that have neuropsychiatric disorders are limited to a handful of antipsychotics. In addition to the differences observed in treated vs. untreated schizophrenics, there are also

controversies regarding the oxidative stress status in patients treated with typical vs. atypical antipsychotic (1).

There is also some evidence of an impaired antioxidant defense and increased oxyradical mediated cellular injury in patients with non-affective psychoses who have never been treated with antipsychotics. Recently, a new hypothesis combining the facts that antipsychotics enhance striatal glutamatergic neurotransmission by blocking presynaptic dopamine receptors and cause neuronal damage by oxidative stress was presented. The contradicted the idea that oxidative stress in patients with schizophrenia could be exacerbated further by treating them with antipsychotics, which possess pro-oxidant properties, based mostly of some papers reporting some possible oxidative stress induced by typical antipsychotics treatment in both humans. Of these studies, some have been carefully conducted, but majority are open label. Despite the proven efficacy of these drugs, the overall outcome for neuropsychiatric disorders remains suboptimal (101).

Thus, the alternative treatment options are urgently needed. One possible approach may be antioxidant therapy. Clinical trials investigating adjunctive antioxidants in the treatment of neuropsychiatric disorders have utilized vitamin E and C, ginkgo biloba extrac and N- acetyl cysteine (NAC), because they are readily available inexpensive and relative safe. Use of antioxidants for treatment related side effects has been none extensively investigated. The totality of the evidence to date suggests that specific antioxidants such as NAC, may offer tangible benefits for the clinical syndromes of schizophrenia. Vitamin may offer salutary effects on the glycemic effects on antipsychotics. Therapy using antioxidants has the potential to prevent, delay or ameliorate many neuropsychiatric disorders including schizophrenia (13). Supplementation of omega-3 poly unsaturated fatty acids in combination with ascorbic acid and α-tocopherol is effective in improving psychopathology (viz. increased scores on the Brief Psychiatric Rating and the positive and negative syndrome scale (PANSS) in chronic-medicated schizophrenic patients. Atypical antipsychotic medication with ascorbic acid, α-tocopherol and lipoic acid has also been shown to improve the clinical outcome of patients with schizophrenia (102).

Similarly, it has been reported that treatment with Ginkgo biloba extract (a powerful flavonoid antioxidant) and haloperidol results in better PANSS scores. Moreover, treatment with NAC the rate limiting factor in the synthesis of GSH, has been shown to improve core symptoms of schizophrenia (103-105). Considering the previous studies has been suggested that NAC treatment could increase GSH levels, thus improving NMDA reception functioning, which is thought to be reflected by the amplitude of the MMN in schizophrenia (105 and 106). Our previous study was shown that oral supplementation of antioxidants in combination reduces oxidative stress and improves clinical symptoms suggest the application of antioxidant in clinical trials is beneficial to prevent or reduces the progression of disease (107).

Conclusion

Currently, the most robust and multi-dimensional evidence for the pathophysiological involvement of oxidative stress for schizophrenia. However, the exact molecular mechanisms are yet to be determined. Indeed, the maintenance of redox balance within cells is a primary component of homeostasis underlying neuronal survival. It may not be too surprising therefore that any process that leads to a disruption of the redox balance can drastically

interfere with a range of other biochemical processes and result in neuronal deficits and dysfunction.

Oxidative stress involvement offers a novel therapeutic target for schizophrenia, however, only when the mechanisms and involvement of oxidative stress in the pathogenesis of schizophrenia are understood, will approaches to antioxidant therapy be designed effectively and targeted. The practical utility of this theory has already garnered support from the existing literature, which has found benefits from the use of vitamins C and E, EGb, NAC and other antioxidants in psychiatric disorders. Hence, identifying viable therapeutic strategies to restore redox balance and the physiological disturbances that result from oxidative stress provide an exciting opportunity for the treatment and ultimately prevention of schizophrenia. Further clinical evidence is required to consolidate the efficacies of antioxidants for the various conditions, but their potential in acute and maintenance, treatment settings are clearly implied on theoretical grounds. These treatments may be useful in the prevention of long-term sequelae by minimizing cell damage and cell death, as well as primary prevention in vulnerable individuals. There are still too few data on the role of essential fatty acid supplementation in the treatment of patients with schizophrenia and larger, well designed clinical studies need to be conducted. The use of antioxidants in their treatment is both substantiated and promising, in view of the internally consistent theoretical framework, convincing early evidence, wide-ranging potential therapeutic benefits, the high population prevalence and overall disease burden associated with these disorders, and the limited efficacies of existing pharmacotherapy. As such, there would seem to be no harm in supplementing a diet with antioxidants. Finally, the mechanism and involvement of oxidative stress in the pathogenesis of schizophrenia needs to be well understood, to design effective and targeted approaches to antioxidant therapy. However, whether this will prove to be the elixir of longevity remains difficult issue to answer accurately.

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