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Review Article

Neuropsychiatric disorders and antioxidant vitamins E and C supplementation

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ABSTRACT

The pathogenesis of neuropsychiatric disorders is incompletely understood, which may partly account for the persisting dominance of the syndrome nosology in neuropsychiatry, despite its widely recognized inadequacies. Oxidative stress mechanism have been implicated in the pathogenesis has theoretical appeal, as the brain is considered particularly vulnerable to the damage. The oxidative vulnerability of the brain, suggests that oxidative damage may be a plausible pathogenic candidate. Antioxidants have attracted the attention of clinicians due to therapeutic potential. The author presents an overview of the current literature on antioxidants supplementation approach, particularly vitamin E and C and current evidences in the field of neuropsychiatric disorders. Vitamin E and vitamin C are well known antioxidants that are postulated to protect against damage to biological membranes by their ability to scavenge free radicals. Results of vitamin combinations are found promising and further studies on this combination therapy are suggested.

1. Introduction

The multiple disease etiologies that lead to neuropsychiatric disorders, such as Parkinson's and Alzheimer's disease, amyotrophic lateral sclerosis, Huntington disease, schizophrenia, depressive illness and stroke, offer significant challenges to drug discovery efforts aimed at preventing or even reversing the progression of these disorders. Neuropsychiatric disorders lead to increased mortality and morbidity in older patients, and are a great burden on society where there is currently no approved treatment to prevent these diseases from affecting patients.[1]

Oxygen is vital for all living cells whether neuronal or other kinds of cells taking part in tissue formation but on the other hand it is potentially dangerous in excess. Thus, it is kept under tight check of complex system that regulates and monitors the usage and uptake of this essential element.[2] Under normal physiological conditions cells thereby cope with the flux of reactive oxygen species (ROS). ROS play an important role in different physiological processes that include cellular signalization, inflammation and immune defense. Normally, ROS concentrations are relatively small due to the activity of antioxidant protection mechanisms that can be enzymatic and nonenzymatic.[3] Even though ROS are involved in a number of diseases, they are also very pertinent mediators of several normal physiological processes. All of the good ROS are products of turnover in the mitochondrial respiratory chain. The highly reactive nature of singlet oxygen can even be exploited to make reactive peroxides that can serve as antimicrobial agents. Most of the physiological effects are in fact mediated by ROS derivatives of superoxide. Similarly, the superoxide anion ($O2^{-\bullet}$), through its derivative, the hydroxyl radical (•OH), plays an essential role in cell physiology by stimulating the activation of guanylate cyclase and formation of the "second messenger" cGMP in cells and activation of the transcription factor nuclear factor kB (NF-kB) by hydrogen peroxide in

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mammalian cells. Under normal physiological conditions, the NO radical (NO•) regulates the vascular tone by smooth muscle relaxation. Redox-mediated increase in free radicals in the postischemic brains notably leads to augmented expression of several proinflammatory genes whose expression ismediated through the transcription factor nuclear factor-kappa-B or NF-κB. Importantly, NF-κB mediated proinflammatory reactions and innate immune responses are prominent features in cerebral ischemic conditions. Although activation of innate immunity by Toll-like receptors seems to promote regenerative mechanisms, neuronal loss critically involves ROS induced TLR-mediated inflammatory responses during cerebral ischemia.[4]

Overproduction of free radicals can cause oxidative damage to biomolecules, eventually leading to many chronic diseases such as atherosclerosis, cancer, diabetics, rheumatoid arthritis, post-ischemic perfusion injury, myocardial infarction, cardiovascular diseases, chronic inflammation, stroke and septic shock, aging and other degenerative diseases in humans.[5] Antioxidants are classified as exogenous (natural or synthetic) or endogenous compounds, both responsible for removal of free radicals, scavenging ROS or their precursors, inhibiting formation of ROS and binding metal ions needed for catalysis of ROS generation.[5] Oxidative stress describes a condition in which cellular antioxidant defenses are insufficient to keep the levels of ROS below a toxic threshold. This may be either due to excessive production of ROS, loss of antioxidant defenses or both.[6] Because of etiopathogenetic heterogeneity, extensive findings from biological, neurochemical, and neuroimaging studies have not provided conclusive evidence for any specific etiologic theory of neuropsychiatric disorders such as schizophrenia, bipolar disorder, and major depression. The vast majority of research on this area has thus far focused on the monoamine neurotransmitter system. However, increasing evidence indicates that disturbances of antioxidant defense system and presence of oxidative stress can play a part in a wide range of neuropsychiatric disorders, including schizophrenia, major depression, epilepsy as well as Alzheimer's disease.[7] Oxidative stress arises due to disturbed equilibrium between pro-oxidant/antioxidant homeostasis that further takes part in generation of ROS and free radicals those are potentially toxic for neuronal cells.[5] The central nervous system shows increased susceptibility to oxidative stress because of its high oxygen consumption rate (20% of the total oxygen inhaled by the body) that accounts for the increased generation of oxygen free radicals and reactive oxygen substrates like superoxide radical (O_2^-), singlet oxygen ($\uparrow O_2$), hydrogen peroxide (H_2O_2) and hydroxyl radical (OH.). Brain has a low level of anti oxidative defense system. The concentration of various anti oxidative enzymes like SOD, Glutathione peroxidase, Glutathione reductase and catalase is low in brain. The Glutathione (GSH), concentration is also very much reduced in the brain when compared to other various organs in the body. In addition to these factors, brain has high concentration of ascorbate and iron in certain regions, which provide favorable environment for the generation of oxygen free radicals. Brain is also enriched with polyunsaturated fatty acids (PUFA) that render them susceptible to oxidative attack. This burden is increased by a number of factors, including the oxidative potential of monoamines such as glutamate, as well as generation of secondary oxidative cellular insults through the neurotoxic effects of released excitatory amines (particularly dopamine and dopamine) and secondary inflammatory responses. Due to lack of glutathione producing capacity by neuron, the brain has a limited capacity to detoxify ROS. Therefore, neurons are the first cells to be affected by the increase in ROS and shortage of antioxidants and as a result, are most susceptible to oxidative stress. This burden is increased by a number of factors, including the oxidative potential of monoamines such as glutamate, as well as the vulnerability of the brain's lipid components to oxidation (2, 5, 8 and 9).

Although many promising drugs, in particular antioxidants, have been developed and shown to be beneficial to experimental animal models, the results of recent clinical trials investigating these promising drugs have been largely negative. Therefore, the antioxidant therapy is a novel therapeutic strategy and neuroscientists are increasingly interested in the participation of ROS towards the pathology involved in neurodegenerative disorders. It is, however, difficult to determine targets for treatment and to distinguish between what may be harmful or beneficial for the brain, without precise knowledge of the pathways involved in the progression of neuronal diseases.[4]

The endogenous antioxidant defense systems are not always entirely successful. The harmful effect in schizophrenia originating from RS could potentially be relieved by inactivation of RS by nutritional intake of antioxidants and essential fatty acids. This is supported by an experiment on animal model. In rats fed with PUFAs brain SOD activity increased. Vitamins have also been used in clinical trials. A study was performed on patients over 70 years old, who were diagnosed with dementia and other cognitive dysfunctions. An improvement in their cognitive performance was observed, after vitamin C and E were given as food supplements. Of note, a positive response was seen in vascular dementia but not in Alzheimer's disease.[4,5]

In a recent study, Yoshitomi and colleagues have reported the synthesis of pH-responsive nitroxide radical containing nano particles which act as highly efficient scavengers of ROS, thus bringing new hopes for antioxidant therapies.[2–5] In other words, oxidative stress results from the metabolic reactions that use oxygen and represents a disturbance in the equilibrium status of pro-oxidant/ antioxidant reactions

in living organisms. The excess ROS can damage cellular lipids, proteins, or DNA inhibiting their normal function. Because of this, oxidative stress has been implicated in a number of human diseases as well as in the ageing process. The delicate balance between beneficial and harmful effects of free radicals is a very important aspect of living organisms and is achieved by mechanisms called "redox regulation.[8] The term redox signalling is used to describe a regulatory process in which the signal is delivered through redox reactions. Redox signalling requires that the steady state of "redox balance" is disturbed either by an increase in ROS formation or a decrease in the activity of antioxidant system(s). The regulated increase in free radicals (ROS/RNS) leads to a temporary imbalance that represents the physiological basis for redox regulation.[8,9]

1.1. Vitamin E and C supplementation and Neuropsychiatric disorders

Pharmaceutical treatment for millions worldwide who have neuropsychiatric diseases is limited to a harmful of antipsychotics/ antidepressants/antiepileptic drugs. Despite the proven efficacy, the overall outcome of these drugs for neuropsychiatric disorders remains suboptimal. Thus, alternative therapeutic options are urgently needed. Again, in order to develop a rational and effective approach to prevent free radical generation and radical-mediated injury, it is necessary to understand the biochemical process that triggers and controls this radical generation and for this one possible approach may be antioxidant therapy. The several evidence to date suggests that specific antioxidants may offer tangible benefits for the clinical syndromes of neuropsychiatric disorders. Tackling of the free radicals involvement offers a novel therapeutic target in diseases.[10]

Vitamins E and C are scavengers of free radicals and play important roles, beyond their antioxidant properties, in cell function. Natural vitamin E is a mixture of tocopherols (α, β and γ) and tocotrienols (α, β and γ). It is a lipid soluble vitamin, which concentrates mainly in the interior of membranes and blood proteins. It is the major lipid soluble antioxidant in human blood plasma. Vitamin E reacts at considerable rates with a variety of free radical species, with emphasis on lipid peroxyl radicals formed during lipid peroxidation. Alpha-tocopherol that interacts with cell membranes, traps free radicals, and interrupts the chain reaction that damages cells. Although no benefit was noted in a study of alpha-tocopherol in patients with Parkinson's disease, there is much interest in a possible role of antioxidants in delaying the onset of Alzheimer's disease.[9,11] Vitamin E, for example, can act under special conditions as a pro-oxidant and not as an antioxidant. Such a condition takes place in vitro in the presence of su&cient amounts of vitamin E with concomitant depletion of other antioxidants that are necessary for vitamin E reduction, like ascorbate.[12]

Vitamin C or ascorbic acid is a water-soluble vitamin that reacts with several radical species producing semidehydro-ascorbic acid or ascorbyl radical. Vitamin C can interact with the tocopherol radical to regenerate reduced tocopherol. Vitamin C is water soluble and can directly react with superoxide, hydroxyl radicals, and singlet oxygen.[2,4,13]

Antioxidant vitamins E and C are important for vascular and brain function and may be capable of quieting activated glial cells in the brain, and/or reducing the oxidative-mediated damage; the latter may be relevant to ameliorate or delay the damage caused by inflammatory processes in neuronal cells. These two vitamins may therefore have important effects on the rate of progression of neurodegenerative disease and on cognitive performance.[14]

There is accumulating evidence in neuropsychiatric disorders of altered antioxidant capacity. Membrane abnormalities can be secondary to free radical-mediated pathology, which may contribute to specific aspects of clinical symptomatology and complications of its treatment. These observations offer an opportunity to develop novel adjunctive therapeutic strategies reducing oxidative stress and repairing membrane deficits. There is evidence that add-on treatment with antioxidant supplementation such as vitamin C, vitamin E, NAC or ginkgo may be beneficial in reducing the schizophrenic Symptomatology.[15] In some study, the administration of antioxidants caused an increase in plasma antioxidant capacity and GSH concentration. Activities of antioxidative enzymes SOD and GSHPx remained constant and, they did not find their increased activity. Nevertheless, their patients had chronic renal failure. In accordance with the improvement of antioxidative defense, they found a lower malondialdehyde (MDA) level following supplementation with antioxidants as a result of a reduced lipid peroxidation degree. These findings could also be expected and are in agreement with administration of antioxidants in other clinical situations characterized by overproduction of free radicals.[15]

Vitamin E and C are suitable for human clinical trials because they are readily available, inexpensive and relatively safe.[10] Hence, identifying useful therapeutic strategies for restoring redox balance and the physiological imbalance that may resulted from oxidative stress provides an exciting opportunity for proper treatment and ultimately prevention of neuropsychiatric disorders. Recent therapeutic approaches for the treatment of neuropsychiatric disease are limited and provide transient benefits to the patients and no any proper attenuation towards further loss of neuronal cells in these conditions. Because neuropsychiatric diseases have a multi-factorial origin, it is not surprising that the current drug design paradigm of 'one-drug-one-target' may not be a sufficient model to develop treatment regimens for these types of diseases.[1] The endogenous antioxidant defense systems are not always entirely successful. The unfamiliar

mechanisms of action of antioxidants to clinical psychiatry may thus have contributed to their peripheral therapeutic status. Furthermore, the heterogeneity within antioxidants as a class is not widely appreciated. Difference exists among the antioxidants in their targets of action as well as in their pharmaco-kinetic properties. The dietary antioxidants vitamin E and C appear to be safe and free of serious adverse effect when used at high doses in adults.[16–18]

Again individual antioxidants may have differential effects in protecting nucleic acids, proteins and lipids from free radical damage and some compounds may be preferentially localized within specific organelles. Thus, rational combination therapy using different and potentially synergistic free radical scavengers could be superior to single agents, although this approach has rarely been used in the trials of antioxidant therapy. The use of vitamin E and C together may be superior to either agent alone.[19] Several studies have examined the efficacy of vitamin E or C in the treatment of neuropsychiatric disorders. The combination of eicosapentanoic/docosahexaenoic acid and vitamin E/C resulted in a significant reduction of schizophrenia psychopathology suggesting that essential PUFA supplementation could represent a very effective treatment to improve the outcome of the disease for an extended period of time.[20]

Vitamin E is a potential to prevent oxidative damage. However, vitamin E cannot prevent oxidative damage to cytosolic proteins, mitochondria and nuclei, where most of ROS are generated. Therefore, it may be important to use vitamin E in combination with vitamin C, a water soluble antioxidant.[13] Oral supplementation of vitamin C with atypical antipsychotics reverse the ascorbic acid levels, reduces oxidative stress and improves BPRS score, hence both the drugs in combination can be used in the treatment of schizophrenia.[21] Supplementation with vitamin C, an effective intracellular antioxidant, has not yet been tried, although its use in preventing intracellular peroxidative injury and restoration of active vitamin E for prevention of membrane lipid peroxidation has been suggested.[20] Vitamin E or C alone has reported inconsistent and variable improvements in biochemical and clinical measures.

Most of the papers hereby reviewed checked the efficacy of antioxidants in the treatment of neuropsychiatric diseases. Although some showed a degree of efficiency when used in animal models or in small clinical studies none of the antioxidants were examined in a large scale controlled study and the data is conflicting.[22] As far as vitamin C is concerned, there is very little data. Available studies with vitamin C treatment and treatment with combinations of vitamin C and vitamin E show a significant improvement in BPRS score and reduction in dyskinetic movement total score.[23]

1.2. Antioxidants supplementation and Schizophrenia

In studies on patients with schizophrenia, the most commonly used antioxidants were vitamins E and C. Vitamin E is a lipid soluble antioxidant able to prevent the oxidative damage. Nevertheless, it has a small potential in preventing oxidative damage to cytosolic proteins, mitochondria, and nucleus, where most of the RS are produced. Therefore, it is reasonable to add vitamin C, a water soluble antioxidant. The adjunctive use of vitamins C and E in schizophrenia requires caution since a high dietary intake will result in pro-oxidant rather than antioxidant actions.[23]

Sivrioglu et al. (2007) and Arvindakshan et al (2003a) found that symptomatic improvement after vitamin E/C supplementation along with omega-3 fatty acids[20–24] Dakhale et al. (2005) reported that supplementation of vitamin c adjunctive to antipsychotic treatment reverse the levels of MDA and ascorbic acid and improvement in BPRS.[21] However, Straw et al. (1989) found that no significant symptomatic improvement in schizophrenics who received ascorbic acid adjunctive to haloperidol.[25]

We find it surprising that two different studies of Adler et al, conducted with the same dose of vitamin E, had opposing results. The former study was conducted with a much smaller number of patients, 28 in comparison to 158 in the later study. Furthermore, the second study lasted much longer, 2 years in comparison to 12 weeks in the first study. In spite of this, the second study showed no significant influence of vitamin E on involuntary movement symptoms, as was observed in the first study. This suggests that there must be some difference in the chosen patient population.[26]

Nicolaus et al. (2002) found that combined supplementation of vitamin E and C helps in reduction of dyskinetic movement total score. The study also suggested that it is reasonable to add vitamin C, a water soluble antioxidant. The adjunctive use of vitamins C and E in schizophrenia requires caution since a high dietary intake will result in pro-oxidant rather than antioxidant actions.[27]

Sajjad et al (1998), Dabiri et al (1994) and Elkashef et al. (1990) reported that vitamin E supplementation shown significant reduction of abnormal involuntary movement syndrome (AIMS)[28–30] however Lam et al (1994) found no significant reduction of AIMS in their 6 weeks trial study.[31]

1.3. Antioxidants supplementation and Major Depression

Opportunity arose to test the hypothesis that antioxidants supplementation would be helpful in subjects with major depressive disorders.[32] Currently, different therapeutic regimens are employed to treat depressive disorders, but their clinical uses are limited by their side effects such as psychomotor impairment, potentiating of other central depressant drugs and dependence liability.[33]

Increasing evidence suggests an anti-oxidative role of antidepressants. Via complex interactions with growth factors, antidepressants seem to help regaining the so-called "oxidative balance".

Bilici et al. (2001), Khanzode et al (2003), Herken et al (2007) demonstrated reversal of antioxidant and oxidative disturbances after antidepressant treatments has provided evidence for the antioxidant effects of these drugs.[34–36] However, studies have not been unanimous in associating normalization of oxidative parameters with antidepressant treatment. One study found 6 weeks of treatment did not affect antioxidative systems small duration of antidepressant treatment.[37,38]

Sarandol et al (2007) reported that oxidative-antioxidative system does not affected by 6 weeks of antidepressant treatment.[38] Ghodake et al (2012) observed after 12 weeks antidepressant treatment that adjunctive to antioxidant vitamin E and C supplementation showed reverse changes in above parameters significantly. Major depression is accompanied by imbalance in pro- and anti-oxidative processes and finally, combined therapy with antioxidants and antidepressant has an improved potential in preventing oxidative damage and repairing already existing damage.[39] However, evidence from cell and clinical models as well as clinical data shown that antioxidant properties of antidepressant. Some studies suggested that the addition of antioxidants or anti-inflammatory drugs enhance the antioxidant properties of antidepressant and produce a better clinical outcome.[37]

Another study investigated the influence of ascorbic acid (which is an antioxidant with antidepressant-like effects in animals) on both depressive-like behaviour induced by a chronic unpredictable stress (CUS) paradigm and on serum markers of oxidative stress and in cerebral cortex and hippocampus of mice.[40]

1.4. Antioxidants supplementation and Epilepsy

Several studies have demonstrated that persons with epilepsy and using antiepileptic drugs have increased oxidative stress.[41] Alpha tocopherol prevents the development of iron-induced epileptic seizures and may be a rational and practical way to prevent PTE. At present, the conventional antiepileptic drugs show partial or no efficacy in the treatment of some forms of refractory epilepsy such as Temporal Lobe epilepsy (TLE).[42]

Kiasalari et al (2012) found that pretreatment with vitamin E decreases the convulsion intensity in kainic acid-induced epilepsy in rats.[43] El-Sebaie et al (2006) reported that vitamin E supplementation led to improvement in EEG background and epileptiform activity in 60% patients, improvement in background activity only in 20% of cases, no response in 10% and deterioration in another 10 % cases. The study also suggested that the use of antioxidant therapy whether melatonin or vitamin E led to reduction of level of NO metabolites and improvement of the clinical condition and EEG record in a large number of patients and thus we consider NO in this study as a pro-pro-convulsant.[44] This study corresponds to those of Tupeev et al (1993) stated that treatment of vitamin E in a dose of 600 mg daily leads to improvement of EEG change and reduction in the number of fits within 4 weeks.[45] Cardenas-Rodriguez et al (2013) suggesting that Given the lack of alternatives for patients with refractory epilepsy, the use of antioxidants should certainly be considered as a therapeutic alternative.[46]

1.5. Antioxidants supplementation and Alzheimer's disease

There is neither proven effective prevention for Alzheimer disease nor a cure for patients with this disorder. Nevertheless, a spectrum of biopsychosocial therapeutic measures is available for slowing progression of the illness and enhancing quality of life for patients. These measures include a range of educational, psychological, social, and behavioral interventions that remain fundamental to effective care. Also available are a number of pharmacologic treatments, including prescription medications approved by the US Food and Drug Administration for Alzheimer disease, "off-label" uses of medications to manage target symptoms, and controversial complementary therapies.[47] There is evidence that vitamins that increase the levels of brain catecholamines and protect against oxidative damage may reduce the neuronal damage and slow the progression of Alzheimer's disease.[11]

The discovery of the neurotoxicity of oxidative free radicals in Alzheimer disease led to a number of trials of antioxidant vitamins, which have had mixed and confusing results. Several studies using vitamin E in doses as high as 2000 IU daily failed to demonstrate improvement in cognition or overall function. Recent evidence indicates that, at high doses, vitamin E may aggravate vitamin K-deficient coagulation disorders and increase all-cause mortality in elderly patients.[47] Petersen et al (2005) found that vitamin E had no benefit in patients with mild cognitive impairment[48] whereas, Engelhart et al (2002) found that high intake of vitamin C and vitamin E from food may be associated with a lower incidence of Alzheimer's disease after a mean follow up period of 6 years. The study suggested that higher intake of vitamin E and vitamin C from food may be associated with a lower risk of Alzheimer's disease. Whether this reflects a causal association remains to be elucidated. Randomized controlled trials can help to evaluate a possible causal relationship between antioxidant intake from supplements and risk of Alzheimer's dis. However the effect of short-term supplement use in clinical trials may not be comparable with long term intake from dietary sources. Therefore more studies are needed to further investigate the association between dietary antioxidant intake and risk of Alzheimer's

disease.[49]

Masaki et al. (2000) and Broe et al. (1990) showed no association between supplement intake and Alzheimer's disease[50,51] while study by Morris et al (1998) found that use of supplements, in particular vitamin C but not vitamin E, was associated with a lower risk of Alzheimer's disease.[52] Sano et al. (1997) reported that treatment with α-tocopherol in patients with moderately severe impairment from Alzheimer's disease slows down the progression of disease than in patients who took placebo. The findings reflect an aberration in the placebo group is unlikely, since the patients in this group reached the end points at the same rate as patients in other multicenter studies. This finding also suggests that the use of selegiline or α-tocopherol may delay clinically important functional deterioration in patients with Alzheimer's disease. One can only speculate about the mechanism underlying this effect. Selegiline may have enhanced the functioning of nigral neurons or enhanced their survival by inhibiting oxidative deamination. Vitamin E may have provided the same benefit, resulting in the inability to observe an additive effect in the group receiving combined treatment.[11]

2. Conclusion

At present, there is no sufficient data with proper evidences that recommended antioxidant supplements for patients with neuropsychiatric disorders is available. Some researchers have been suggested that mega doses and long-term use of antioxidant vitamins can be harmful. There is an ocean of information available on different treatment methods such as Ayurvedic medicinal herbs, Western herbs, Chinese herbs, vitamins and all other kinds of supplements but often the information given are not precise and complete enough to help the consumer to do a correct and conscious use of the supplemented antioxidants. Results of vitamin combinations are found promising and further studies on this combination therapy are suggested. Because, still there is lack of sufficient data as concern, combined vitamin E and C supplementation. However, despite the fact that the available data suggests the use of combined vitamin E and C supplementation can modulates oxidative stress represents an exciting and useful opportunity for prevention and treatment of neuropsychiatric disease. Further, it gives an idea for future studies for carefully determination regarding which antioxidants, at what dosage, at what duration and in what combinations will have the greatest therapeutic benefit with the least risk, considering the importance of free radicals in many biochemical reactions.

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4. Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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