

“Homocysteine-Induced Neurotoxicity and Oxidative Stress in Neuropsychiatric Disorders.”

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Abstract: The author presents an overview of the current literature on homocysteine as a risk factor for neuropsychiatric Disorders. The neuropsychiatric literature has recently seen a spate of papers on the role of homocysteine, a sulfur-containing amino acid that is not a dietary constituent and does not form proteins. Epidemiological evidence has gradually accumulated to implicate homocysteine in the pathophysiology of many neuropsychiatric Disorders. However, pathogenic mechanisms that increase oxidative stress by homocysteine are unsubstantiated. Homocysteine induces oxidative stress by up-regulating promoting reactive oxygen species (ROS) production by increasing NADPH oxidase and decreasing thioredoxin. Increased oxidative stress via ROS also increases inducible nitric oxide synthase (iNOS) expression and subsequent nitrotyrosine formation. The findings which establish a link between oxidative stress and hyperhomocysteinemia have inspired a number of other recent studies focusing on the link between oxidative status and neurotoxicity in neuropsychiatric disorders. This review examines the discoveries made on the neurotoxicity due to homocysteine-induced oxidative stress and also discussed the therapeutic approach of antioxidants in neuropsychiatric disorders along with hyperhomocysteinemia.

Key words: Oxidative stress, homocysteine, antioxidants, reactive oxygen species, neuropsychiatric disorders.

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I. Introduction

Homocysteine, a sulfur-containing non-standard amino acid, not a dietary constituent and does not used for protein synthesis. It was discovered by an American biochemist de Vigneaud, in 1932, named it homocysteine, as its structure was found to be similar to cysteine with an extra carbon atom. Homocysteine is exclusively derived from the demethylation of methionine. Methionine is an amino acid found plentiful in both plant and animal proteins and the main source of protein sulfur atoms (1). The demethylation reaction is a vital metabolic pathway resulting in methylation reactions in the body. The produced homocysteine is either remethylated to methionine, a pathway that utilizes folate and vitamin B₁₂ as cofactors, or directly catabolized by trans-sulfuration into cystathionine if excess homocysteine is present, using vitamin B₆ as a cofactor. Three main enzymes are involved in the metabolism of homocysteine: methionine synthase (MS) and 5-methyltetrahydrofolate reductase (MHTFR) in the re-methylation, and cystathionine β-synthase (CBS) in trans-sulfuration. These enzymes, along with the coenzymes, maintain the intracellular concentration of homocysteine within a narrow range, even though the plasma levels vary considerably (2, 3).

Homocysteine exists in different forms. It is present as the reduced form with a free sulfhydryl (SH) group, as homocysteine or the oxidized form with the disulfide (S-S) linkage, as a dimer with cysteine and as adducts. The adducts are formed by N-homocysteinylolation where homocysteine thiolactone binds to lysine residues of proteins. Homocysteine thiolactone is formed by methionine tRNA synthetase when homocysteine is mistakenly selected by the enzyme in place of methionine during protein biosynthesis. Homocysteine, homocysteine dimer, homocysteine thiolactone and homocysteine adducts form the total homocysteine. The concentration of the three forms is low and that of homocysteine adducts (Homocysteine thiolactone form bound to proteins) is very high in plasma (4). Homocysteine indirectly participates in methyl, folate and cellular thiol metabolism (5).

However, homocysteine metabolism in brain is different as compared to the other organs. The trans-sulfuration pathway is inactive while the methylation pathway that using betain is absent. The capacity for homocysteine metabolism is mostly dependent on the supplies of folate and cobalamine. The glial cells are the very low stores of vitamin B₁₂ that can be quickly depleted during its negative balance. In addition, adenosyl

cobalamine is a co-factor, so there is methyl malonic aciduria due to deficiency of B₁₂. Methyl malonic acid is neurotoxic molecule and it may develop symptoms like mild irritability, mood swings and forgetfulness to depression and dementia (2).

Again, homocysteine (with -SH group) continuously gets oxidized to produce homocysteine (S-S group) and homocysteinylated proteins. This leads to the formation of ROS such as superoxide, hydrogen peroxide and hydroxyl radicals. The adverse effects of ROS on bio-molecules (proteins, lipids) are well known. Further, superoxide converts nitric oxide to peroxynitrite also depleting the tissue NO[•] levels (2, 3).

In addition to the known impact of homocysteine on the cardiovascular system and micro-nutrient biochemical pathways, numerous diseases of the nervous system are correlated with high homocysteine levels and alterations in B₁₂, folate, or B₆ metabolism, including Depression, Schizophrenia, Parkinson's disease, Multiple sclerosis, Cognitive decline and Alzheimer's disease in the elderly (6).

Homocysteine induces NADPH oxidase and increases ROS. Again homocysteine continuously oxidized resulting homocysteine (S-S group) and homocysteinylated proteins. This leads to formation of ROS. Further superoxide converts NO[•] to peroxynitrite thereby depleting NO[•] levels affecting endothelial functions (2). However, it was unclear whether the increase in ROS was secondary to a decrease in thioredoxin by homocysteine. It was demonstrated that homocysteine instigated oxidative stress, in part, by decreasing thioredoxin. Homocysteine activates PAR-4, which induces production of ROS by increasing NADPH oxidase and decreasing thioredoxine expression and reduces NO bioavailability in cultured MVEC by 1) increasing NO-2 tyrosine formation and 2) accumulating ADMA by decreasing DDAH expression (7).

II. Homocystein, Oxidative Stress and CNS

Homocysteine can be condensed with serine to form cystathionine in a reaction that uses vitamin B₆. Methionine is subsequently metabolized into SAM. This metabolite is involved in numerous methylation reactions, involving proteins, phospholipids, DNA, and neurotransmitter metabolism. So it is not surprising to suspect the role of homocysteine in the neurological and psychiatric disorders, where the central neurotransmitters are known to be altered. Alteration in the level of homocysteine, either because of genetic abnormalities or due to the acquired/ environmental influences like low intake of vitamins involved in the metabolism, would theoretically correlate with the neurochemical abnormalities seen in the various neuropsychiatric disorders (8).

The idea that homocysteine can promote formation of free radicals is supported in the majority of cases with only indirect evidence. Toxic effects of homocysteine are mediated especially by free radicals, although some studies do not support this hypothesis (4). It has also been found that homocysteine is neurotoxin, especially in conditions in which excess glycine levels are including head trauma, stroke and vitamin B₁₂ deficiency. Also, homocysteine causes the release of several inflammatory mediators that play an active role in atherosclerotic plaque formation. These are tumor necrotic factor α (TNF α) and receptor for advanced glycation end-products (RAGE) and its signal transducing ligand (1). In addition, homocysteine may augment β -amyloid neurotoxicity by additional mechanisms independently of calcium influx (9).

Homocysteine may interact with the N-methyl-D-aspartate (NMDA) receptor, causes excessive influx of calcium and free radical production, resulting in neurotoxicity. The neurotoxic effects of homocysteine include reduction in methylation reactions in the CNS that may contributed to the mental symptomatology as seen in B₁₂ and folate deficiency (10).

Research studies have yet to be convincingly demonstrated the role of homocysteine in the pathogenesis of various mental disorders. The findings reflected partial, episodic, and sometimes even weak clinical correlations between hyperhomocysteinemia and psychiatric disease (4). Some findings recommended more prospective studies, and perhaps placebo-controlled intervention studies to definitely establish the relationship between homocysteine and neuropsychiatric disorders (11).

Some of the studies suggested that hyperhomocysteinemia, at least in females, is an unspecific risk factor for dementia and depression (organic brain disorders), but not endogenous psychosis like schizophrenia (12). Other study described a similar correlation between elevated homocysteine levels and cerebral atrophy in healthy elderly individuals, suggesting that hyperhomocysteinemia is neurotoxic (1).

III. Homocysteine and Schizophrenia

Elevated plasma homocysteine concentration has been suggested as a risk factor for schizophrenia, but the results of epidemiological studies have been inconsistent (13). Results of few studies showed that homocysteine metabolism and monoaminergic neurotransmitter systems are important in schizophrenia pathology. Moreover, some results suggest that association of homocysteine with schizophrenia may involve the glutamatergic system. Homocysteine may act as an antagonist at the glycine site of the NMDA receptor (in the presence of normal or low glycine levels) or it may act as an agonist at the glutamate site of this receptor (when glycine levels are increased) (5).

Homocysteine may also enhance oxidative stress **Dietrich-Muszalska et al (2012)** showed that in schizophrenic patients the amount of homocysteine in plasma was higher in comparison with controls. Moreover, results indicated the correlation between the increased amount of homocysteine and the oxidative stress exists (7). Considering the data presented in this study, we suggest that the hyperhomocysteinemia in schizophrenic patients may stimulate the oxidative stress.

Dietrich-Muszalska et al (2009) suggested that increased homocysteine may have a significant influence on the development and clinical symptoms of schizophrenia. In fact, oxidative modifications of proteins, measured by 3-nitrotyrosine and carbonyl groups, are proven to be significantly increased in schizophrenia due to elevated levels of homocysteine (14). A study by **Brown AS et al (2007)** reported that higher maternal levels of homocysteine may be a risk factor for schizophrenia. Specifically, mothers that have an elevated third trimester homocysteine may increase the chances of schizophrenia through developmental effects on brain structure and function and / or through subtle damage to the placental vasculature that compromises oxygen delivery to the fetus (15). **Haidemenos et al (2007)** observed that patients with chronic schizophrenia had increased the amount of plasma homocysteine compared to controls, but this increase in plasma homocysteine levels is not related to plasma folate and vitamin B12 levels (16).

Pasca et al (2006) found that high levels of homocysteine are negatively correlated with glutathione peroxidase activity, suggesting that high levels of homocysteine may also associate with oxidative stress in schizophrenia (17). **Nevo et al (2006)** showed that the associations between homocysteine level and schizophrenia in adolescents by using numerically small groups of patients (aged 14-21 years). It was observed that higher homocysteine level in patients with schizophrenia than in healthy control-group patients; however, this concurrence has been found only in boys (18). The finding of **Muntjewerff et al (2006)** provides the evidence for an association of homocysteine with schizophrenia. Risk elevation of schizophrenia associated with the homozygous genotype of the MTHFR 677C>T polymorphism provides the support for causality between a disturbed homocysteine metabolism and risk of schizophrenia. The performed meta-analyses showed no evidence of publication bias or excessive influence attributable to any given study (13).

Goff et al (2004) found increased homocysteine concentration which correlated with severity of extrapyramidal symptoms. While, the homocysteine concentration did differ between men and women but did not correlate with age or number of cigarettes smoked daily and did not differ significantly from the value for the Framingham Offspring Study (19). **Levine et al (2002)** showed that increased plasma homocysteine levels in schizophrenia to include a range of age groups. The difference between groups was almost entirely attributable to the homocysteine levels of young male patients with schizophrenia. Elevated levels of homocysteine in young male patients with schizophrenia could be related to the pathophysiology of aspects of this illness (20). **James et al (2002)** reported that high homocysteine concentration have been shown to be accompanied by high S-adenosyl homocysteine levels suggested to be associated with DNA hypomethylation and alteration in gene expression in schizophrenia (21). **Virgos et al (1999)** found no difference in the plasma homocysteine levels of schizophrenic's inpatients and comparison subjects with the average age both subjects was over 60 (22) whereas, **Regland et al (1995)** suggested that an increased level of homocysteine is common feature in schizophrenics (23).

IV. Homocysteine and Major Depression

There is strong published evidence for the association between homocysteine level and depression, vascular disease, and neurotransmitters. The most direct evidence for the association between homocysteine and neurotransmitters is from a study showing that depressed patients with increased total plasma homocysteine levels had significantly lower levels of serum, red cells, and CSF folate, as well as lower levels of CSF S-adenosylmethionine (SAME) (24).

Gariballa et al (2011) observed lower plasma total homocysteine concentrations were associated with reduced depression symptoms in older patients recovering from acute illness. The mean total homocysteine concentration fell by 22% among patients given the supplements compared with the placebo group (mean difference 4.1 $\mu\text{mol/L}$. total homocysteine concentrations was divided into four quartiles and analyzed against depression scores. Total homocysteine concentrations in the first relative to the fourth quartile of the distribution were associated with lower depression symptoms at the end of the supplement period (25).

Almeida et al (2008) suggested that the triangular association between MTHFR genotype, total homocysteine and depression implies that higher concentration of homocysteine increases the risk of depression and that lowering the total homocysteine by 0.19 mg/L could reduce odds of depression about by 20% (26). **Sachdev et al (2005)** suggested that folic acid deficiency and high homocysteine, but not low vitamin B₁₂ levels, are correlated with depressive symptoms found in community-dwelling middle-aged individuals. The overlapping but distinct effects of folic acid and homocysteine were observed. Also, homocysteine levels had a significant linear relationship with depressive symptoms score in men but not in women. The findings in sub-

syndromal depression also suggested that there may be a role for folic acid per se in the prophylaxis of depression and the beneficial effect may not be restricted to the elderly population (27).

Tiemeier et al (2002), **Naismith et al (2002)** and **Fava et al (1997)** showed that hyperthermia, vitamin B12 deficiency and to a lesser extent folate deficiency were related to depressive disorders (28, 29, 30) while, **Hickie et al (2001)** reported that higher rates of C677T MHTFR mutation in late onset depression compared to early-onset depression, but total homocysteine levels were not reported (31). **Bottiglieri et al (2000)** studied 46 inpatients for depression, about one half had elevated homocysteine levels compared with controls, with only a few subjects with low red cells folate, and subjects with high homocysteine levels had more severe Hamilton Depression Rating Scale (HDRS) scores (32).

Studies by **Morris et al (2003)** and **Penninx et al (2000)** suggested that there is no association between hyperhomocysteinemia and depression (33, 34) whereas **Severus et al (2001)** suggested that higher levels of homocysteine may play an important role in the elevated risk of cardiovascular mortality in depression (35). **Bryer et al (1992)** found that homocysteine and stroke might causes depression by alteration of neurotransmitters. Specifically, showed that depressed patients with increased total homocysteine levels and significantly lower levels of serum red cells and CSF folate, as well as lower levels of CSF S-adenosyl methionine. Evidence for the association between homocysteine and neurotransmitters is found in study indicated that directly measure neurotransmitter metabolites and the antidepressant effects of folate and S-adenosylmethionine, a cofactor and an intermediate metabolite of the methionine-homocysteine pathway (36).

V. Homocysteine and Epilepsy

Epileptic seizures are caused by the pathological stimulation or lack of stimulation of nerve cells. NMDA receptor play an important in the generation and maintenance of epileptic seizures homocysteine and other S-containing metabolites can induce epileptic seizures by NMDA receptor activation (37). It was observed that in experimental animal models that, systemic administration of high doses of homocysteine in animals produce convulsive seizures (38, 39).

Paknahad et al (2012) showed no difference in homocysteine levels in epileptic and non-epileptic groups, although the means of the serum folic acid were similar. It was reported that AEDs induces hyperhomocysteinemia might be through the dysfunction of homocysteine metabolism, the acceleration of vitamin metabolism, and the possible interference in the metabolism of folic acid coenzymes (40). **Siniscalchi et al (2012)** suggested that treatment with antiepileptic drugs (AEDs) in Down syndrome with epilepsy group (DSEp,) patients induces an increase in plasma homocysteine levels and a significant decrease in serum folic acid, therefore supplementation with vitamins may be useful in order to obtain normal plasma homocysteine values and reduce the risk of both cardiovascular and neurological diseases (41).

The spectral and clinical investigation by **Bright et al (2010)** showed that the addition of vitamin B₆ and B₁₂ can markedly decreased plasma homocysteine levels in plasma. The FTIR spectra were recorded at the end of the first and the second month and also the homocysteine levels were clinically tested. The absorption values of the specific modes of vibration pertaining to Homocysteine of both pre and post-treatment spectra were noted and the percentage of efficacy of the multivitamins was calculated (42). **Monji et al (2005)** reported that an antiepileptic drugs can raise homocysteine concentration can represent a risk factor for the occurrence of interical (occurring between seizures) psychosis (43). **Huemer M et al (2005)** showed that hyperhomocysteinemia was present in 15.5% of children receiving long-term AED treatment. Multidrug treatment and long duration of therapy enhance the risk for hyperhomocysteinemia was observed. Folic acid supplementation significantly reduces total homocysteine (44). **Kubva et al (1995)** and **Mudd et al (1985)** studied that administration of high doses of homocysteine to animals resulting in convulsive seizures but, the relationship with lower Homocysteine has not been established (39, 45).

VI. Homocysteine and Alzheimer's Disease

The cause of neuronal degeneration in Alzheimer's disease (AD) has not been completely clarified, but has been variously attributed to increases in cytosolic calcium and increased generation of reactive oxygen species (ROS). The β -amyloid fragment (A β) of the amyloid precursor protein induces calcium influx, ROS and apoptosis. Homocysteine, a neurotoxic amino acid that accumulates in neurological disorders including AD, also induces calcium influx and oxidative stress, which has been shown to enhance neuronal excitotoxicity, leading to apoptosis (9). In cross-sectional studies, elevated plasma total homocysteine concentrations have been associated with cognitive impairment and dementia. Incidence studies of this issue are few and have produced conflicting results (46).

Zhao et al (2013) showed that the serum levels of Homocysteine in hyperlipidemia group with Alzheimer's disease (AH), Alzheimer's disease group without hyperlipidemia (A), and hyperlipidemia group without Alzheimer's disease (H), groups are significantly higher than that of in normal group without Alzheimer's disease (N). The serum levels of homocysteine in AH and an H group is significantly higher than

that of in A group. There was no significant difference found between A group and AH group. MMSE score for Alzheimer's disease has negative correlation with serum level of homocysteine. These results indicate that hyperlipidemia contributes to Alzheimer's disease by elevated plasma homocysteine and elevated plasma homocysteine enhanced oxidative stress by lipid peroxidation in Alzheimer's disease with hyperlipidemia (47).

Nikanfar et al (2008) showed that the average serum homocysteine level in Alzheimer patients was higher than control group, but did not show a significant relationship with the severity of illness. The relationship between Mini Mental State Examination (MMSE) score and serum homocysteine levels of patients was not significant (48).

Haan et al (2007) reported in the Sacramento Area Latino study on Aging reported that, an association between higher homocysteine levels and a combined outcome of cognitive impairment no dementia and dementia (49). **Dorszewska et al (2007)** suggested that increased plasma levels of homocysteine in Alzheimer's disease and lowered methionine and homocysteine ratio. This may indicated that Alzheimer's disease could have developed due to altered processes of homocysteine remethylation to methionine and trans-sulfuration to cysteine. The decrease in methionine and homocysteine ratio may be linked to transformation of homocysteine to thiolactone in endothelial cells (50). **Mooijaart et al (2005)** found elevated serum concentration of homocysteine were associated with an increased rate of cognitive decline indicating that high homocysteine may be a consequence, but not cause of the disease (51) whereas, in several studies by **Gunstad et al (2006)**, **Ariogul et al (2005)** and **Kalmijn et al (1999)** showed hyperhomocysteinemia but homocysteine levels were not associated with cognitive impairment (52, 53, 54). **Ravaglia et al (2005)** showed elevated plasma total homocysteine concentrations and low serum folate concentrations are independent predictors of the development of dementia and Alzheimer's disease. These findings indicating that hyperhomocysteinemia doubles the risk of developing dementia and Alzheimer's disease independently of several major confounders (46).

Seshadri et al (2002) found that an increased plasma homocysteine level is a strong, independent risk factor for the development of dementia and Alzheimer's disease. The study indicates that there is a strong, graded association between plasma total homocysteine levels and the risk of dementia and Alzheimer's disease. An increment in the plasma homocysteine level of 5 μmol per liter increased the risk of Alzheimer's disease by 40 percent. A plasma homocysteine level in the highest age-specific quartile doubled the risk of dementia or Alzheimer's disease. A similar result was found when the single criterion of hyperhomocysteinemia (baseline plasma homocysteine, $>14 \mu\text{mol}$ per liter) was used. The magnitude of this effect is similar to the magnitude of the increases in the risks of death from cardiovascular causes and stroke associated with a similar increment in the plasma homocysteine level (55). **White et al (2001)** suggested that higher copper and/or homocysteine levels in the elderly can promote significant oxidant damage to neurons and represents additional risk factor that produces Alzheimer's disease or related neurodegenerative conditions. The data demonstrated the interactions between homocysteine and copper can result in significant neuronal damage and cell death (56). **Clarke et al (1998)** examined 164 patients with Alzheimer's disease, with histological confirmation in 76 and found that those with baseline total homocysteine in the top two tertiles had significantly more temporal lobe atrophy after three years than those with lowest tertile, suggesting that elevated total homocysteine levels may determine rate of progression of disease (57).

VII. Hyperhomocysteinemia and Antioxidants: Therapeutic Approach

Current therapeutic approaches for the treatment of neurodegenerative disease offer only limited and transient benefits to patients, with no attenuation of the further loss of neuronal cells in these conditions. Because neuropsychiatric diseases have a multifactorial 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 (58).

Free radicals cause oxidative damage to cells and DNA, which can be reduced by antioxidants. Antioxidant nutrients appear to play an important role in protection against various disorders (59). The lipid-soluble antioxidant vitamin E is localized in the cell membrane and has been targeted for its relation to atherosclerosis and vascular function. Decreased concentration of antioxidants including vitamin E in the presence of stimuli such as infection, bacterial colonization, exposure to various toxins, and/or metabolic changes such as increased homocysteine, could increase free radical concentrations and alter normal brain vascular function. Various studies have assessed the effects of vitamin E intake on neurologic function and vitamin E concentration in different brain regions. Vitamin C treatment, through dietary supplementation alone or in combination with anti-inflammatory drugs and/or other antioxidants, may provide valuable protection against the neurodegenerative changes associated with cognitive impairment (60). Evidence from cell and animal models as well as clinical data show antioxidant properties of antidepressants. Some studies suggest that the addition of antioxidants or anti-inflammatory drugs enhance the antioxidant properties of antidepressants and produce a better clinical outcome (61).

Homocysteine levels can be easily reduced by supplementation with folic acid, and to a lesser extent B₆ and B₁₂. Folic acid is far more effective as homocysteine-lowering agent compared with vitamins B₆ and B₁₂ that cause little, if any, reduction in homocysteine. Folate supplementation resulted in a significant increase of its concentration within erythrocytes. Homocysteine concentration significantly decreased due to folate supplementation in accordance with the findings of other authors (62, 63, 64). It was proposed that antioxidant supplementation had no effect on homocysteine concentration. Furthermore, there were no additive effects of antioxidants and folate with respect to an influence on homocysteine levels. The studies also found that both folate and antioxidants improved antioxidative defence and lowered lipid peroxidation in patients with hyperhomocysteinemia, while supplementation with folate only caused a significant decrease of homocysteine concentration. Simultaneous administration of folate and antioxidants resulted in a slower decrease of folate concentration after finishing its supplementation (4).

VIII. Conclusion

The various mechanisms proposed to explain the toxic effects of homocysteine including lipid peroxidation. The present review provides evidence that elevated homocysteine level and the increased oxidative stress contribution. 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. Therefore in the next step the future studies must focus on the role of different antioxidant in the oxidative stress in neuropsychiatric which have elevated homocysteine.

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