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Should Homocysteine be a Therapeutic Target for Neurological Disorders?

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Recent clinical and laboratory findings have attracted much interest in homocysteine (Hcy) because the latter is relevant to numerous medical conditions. Elevated plasma level of Hcy (eHcy) is a recognized independent risk factor for cardiovascular disorders [1,2], causing arthrosclerosis and myocardial infarction. Additionally, eHcy has been observed in a number of neurological disorders including stroke [3], dementia, Alzheimer's disease (AD) [4], Parkinson's disease (PD) [5], and amyotrophic lateral sclerosis (ALS) [6].

Hcy is an intermediate metabolite of the essential amino acid methionine involving DNA metabolism via mythylation. Hcy can be converted into either methionine or cystathione by the enzymes methionine synthase, which requires B12 as a cofactor to remethylate Hcy to methionine, or cystathione β-synthase, which controls trans-sulfuration of Hcy to cystathione and requires B6 as a cofactor; and methyltetrahydrofolate reductase (MTHFR), which requires folate for reaction. In physiologic conditions, Hcy is converted to methionine which is activated by ATP to form S-adenosylmethionine (SAM) and serves as a universal methyl donor. The transfer of SAM's methyl group to an acceptor molecule generates S-adenosylhomocysteine (SAH) which is then hydrolyzed and regenerates homocysteine [7]. This hydrolysis is a reversible reaction that favors the synthesis of SAH which is also a potent inhibitor of methylase enzymes. Thus, an elevated intracellular SAH or a low SAM/SAH ratio may predict methylation deficits [7], which are critical for neurological function. The plasma level of Hcy is determined primarily by adequate dietary intake and vitamin status. eHcy can be caused by either a deficiency of B12 or folic acid alone, or in combination, or genetic factors, such as C667T MTHFR polymorphism.

eHcy likely exerts its adverse effects via direct and indirect intracellular actions. For example, eHcy stimulates free radical production, provokes oxidative stress response, increases cytosolic calcium level, interferes with mitochondrial function, depletes ATP reserve, impairs transmethylation of DNA causing DNA breakage, and results in hypersensitity to excitotoxicity and apoptosis [8-10]. Of note, depletion of cellular ATP is a pivotal factor in neurodegenerative disorders such as AD, PD, ALS, and Huntingdon's disease [11,12]. eHcy may potentiate synaptic glutamate receptor activity either directly [13] or indirectly via its metabolite L-homocysteic acid [14], thereby altering synaptic functions. These actions can be diminished by metabotropic glutamate receptor antagonists [10, 15]. Further, eHcy may compromise anti-oxidative capacity by decreasing glutathione peroxidase activity [16] and tissue levels of vitamins A, C and E [17]. These adverse effects of eHcy on anti-oxidative activity occur at multiple levels and can be modified by administration of N-acetyl-L-cysteine, vitamin C or vitamin E [18]. Interestingly, supplementation of folate is not as effective as N-acetyl-L-cysteine, vitamin C or vitamin E in protecting against Hcy-induced apoptosis [19] but capable of reducing intracellular superoxide levels independently from Hcy levels [20], indicating a different anti-oxidative mechanism of folate from that of Hcy.

Recent studies suggest that eHcy is an independent risk factor for cardiovascular diseases and responsible for about 10 percent of total risk [2]. The relationship between plasma Hcy levels and risk of cardiovascular diseases and stroke is as follows: 7 μM, low; 8-11 μM, moderate; 12-16 μM, high; 16 μM, very high [21]. An increase of 1 μmol/l in plasma Hcy corresponds to a 151 gram decrease in birth weight in the third trimester of Japanese women who's intake of folate was only dietary [22]. Additionally, evidence from clinical studies relating eHcy to neurologic disorders appears to be compelling [3-6,8], though the possibility that eHcy may be related to the side effects of medication, such as levodopa, [5,23] and normal physiologic conditions [3] cannot be dismissed. eHcy may have an uninformed impact on neurodegeneration. Laboratory studies showed eHcy potentiates A_β neurotoxicity in cultured neurons [15]; enhances the susceptibility of dopaminergic neurons to environmental toxic insults such as rotenone, iron, and MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine)-induced dopaminergic neuronal death in a mouse model of PD [24]; and accelerates motor neuronal death [25,26]. Clinical studies have documented that eHcy causes vascular endothelial cells dysfunction leading to hypercoagulation, atherosclerosis and stroke [3], which may, in turn, play a role in the pathogenesis of neurodegenerative disorders [8]. Notably, those neurologic disorders commonly occur in late adult life, which may suggest possible cumulative effects, such as Hcy, from environments with possible genetic predispositions. Importantly, eHcy level is related with various physiologic and pathologic conditions including old age [3], male sex, cigarette smoking [27], chronic renal insufficiency, high blood pressure, elevated cholesterol level, and lack of exercise [28].

Currently there is no cure for neurodegenerative disorders. The best approach in clinical practice is primarily prevention through modification of acquired risk factors. As eHcy may play a role in promoting early onset of various neurologic disorders, exacerbating the symptoms, and accelerating neurodegeneration, eHcy may become a therapeutic target in tertiary management although evidence of Hcy as a definite risk factor for the development of neurodegenerative disorders is still lacking. Nevertheless, information that eHcy may be causally relevant to neurologic disorders could have important clinical implications, because administration of vitamin B-complex with folate to reduce eHcy is inexpensive, potentially effective, and devoid of adverse effects, therefore, having an exceptionally favorable benefit/risk ratio [2,29,30]. However, the efficacy in prevention of neurologic disorders remains to be elucidated and in debate [21]. Well-designed prospective randomized placebo-controlled clinical trials are warranted to evaluate the efficacy of administration of vitamin B-complex with

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folate to patients with eHcy in preventing the onset, or mitigating the severity, of neurologic disorders.

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