N-acetyl-cysteine supplementation lowers high homocysteine plasma levels and increases glutathione synthesis in the transsulfuration pathway. Beneficial effects on several cardiovascular and neurodegenerative diseases

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ABSTRACT

Glutathione (GSH), a compound derived from a combination of three amino acids - cysteine, glycine and glutamine - is the final product of homocysteine (Hcy) metabolism in the transsulfuration pathway. The major determinants of GSH synthesis are the availability of cysteine and the activity of the rate-limiting enzyme, glutamate cysteine ligase. A deficiency in transsulfuration pathway leads to excessive Hcy production (HHcy) and reduced GSH synthesis. This tripeptide, that exists in the reduced or active form (GSH) and oxidized variant (GSSG), is the main antioxidant of the body. Independently of its antioxidant function, the compound has an anti-inflammatory role too, reducing the production of interleukins and the expression of tumor necrosis factor-alfa and iNOS synthase. A dysregulation of GSH synthesis is recognized as contributing factor to the pathogenesis of many pathological conditions. But, the insufficiency of the transsulfuration pathway is also responsible for HHcy. Besides, this condition decreases the activity of cellular *glutathione peroxidase*, an intracellular antioxidant enzyme that reduces hydrogen peroxide to water with the prevalence of GSSG on GSH. The consequent GSH/GSSG impaired ratio also causes some common cardiovascular and neurodegenerative disorders. In both occurrences, N-acetyl-cysteine supplementation supplies the cysteine necessary for GSH synthesis and contemporarily reduces HHcy, improving the GPx1 activity and further reducing oxidative stress.

Introduction

Hyperhomocysteinemia (HHcy) is a medical condition characterized by an abnormally increased plasma concentration of this sulphur-containing amino acid. This metabolic defect can be associated with a number of disease states, such as several cardiovascular disorders and some neurodegenerations.[1-5] Homocysteine (Hcy) can be re-methylated to Methionine by the re-methylation pathway, or further metabolized to cystathionine and glutathione (GSH), by the transsulfuration pathway. In this last pathway, Hcy firstly condenses with serine to form cystathionine, in a reaction catalyzed by means of the enzyme *cystathionine-ß-synthase*. Subsequently, cystathionine reacts with H_2O, through the enzyme *cystathionine-gamma-lyase* and is changed in L-cysteine. Afterwards, cysteine is transformed in gamma-glutamyl-cysteine, by *glutathione synthase,* producing the final compound, *i.e.* GSH. This is important for protein synthesis, detoxification processes, and some metabolic functions,[6,7] in accordance with Figure 1. A dysregulation in transsulfuration pathway, due to the cysteine deficiency or the enzyme glutamate cysteine ligase, leads to excessive Hcy production and reduced GSH synthesis.[8]

GSH is a tripeptide deriving from the sequential addition of cysteine to glutamate. The sulfhydryl group (-SH) of cysteine is involved in reduction and conjugation reactions.[9] The thiol-reduced (or active) form is usually indicated as GSH. On the contrary, in the oxidized form, is monogrammed as GSSG. To function as antioxidant, GSH requires the activity of the enzyme *glutathione peroxidase*. Contrarily, the activity of

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the enzyme *glutathione reductase* acts when GSH is oxidized to GSSG.[10] In turn, oxidative stress rising from GSH to GSSG favors the release of pro-inflammatory cytokines, and tumor necrosis factor-alfa (TNF-alfa).[11] Both oxidative stress and chronic inflammation lead to several cardiovascular and neurodegenerative diseases.

N-acetyl-cysteine supplementation

N-acetyl-cysteine (NAC), commonly used as mucolytic, had been employed for treatment of several diseases in a direct action or in a combination with some other drugs. Among other several functions, NAC is able to stimulate GSH biosynthesis because it supplies the cysteine necessary for that. In addition, NAC is a source of -SH groups, involved in the oxidation-reduction process (cellular respiration).[12] But, NAC supplementation also reduces HHcy plasma levels with not well-defined mechanisms. Ventura *et al.* hypothesized that rapid administration of NAC induces a reduction of Hcy, displacing Hcy from their binding protein sites, forming mixed disulfides (NAC-Hcy), with high a renal clearance.[13] Afterward, other AAs hypothesized that, in patients with end-stage renal disease intradialytic decline of total Hcy, after NAC administration, resulted from the removal of unbound Hcy, whereas the reduction of plasma Hcy after hemodialysis had been attributed to the elimination of uremic toxins, with the inhibitory activity against enzymes involved in the metabolism of Hcy.[14,15] More recently, Hildebrandt *et al.* affirmed that four weeks of oral NAC supplementation significantly decreased plasma Hcy concentration by previously described mechanisms. In this work, NAC supplementation was associated with a 28% average increase in plasma cysteine (that, in turn, increases GSH synthesis) and an approximatively 12% reduction in Hcy serum concentration.[16] Therefore, in the presence of oxidative stress from a deficiency of transsulfuration pathway, NAC supplementation has beneficial effects on the consequent cardiovascular and neurodegenerative disorders.[17-19]

Cardiovascular disorders

Coronary disease

The formation of atherosclerotic plaques inside the coronary arteries, inducing ischemic cardiopathy, is the leading cause of coronary artery disease (CAD).[20] Sev-

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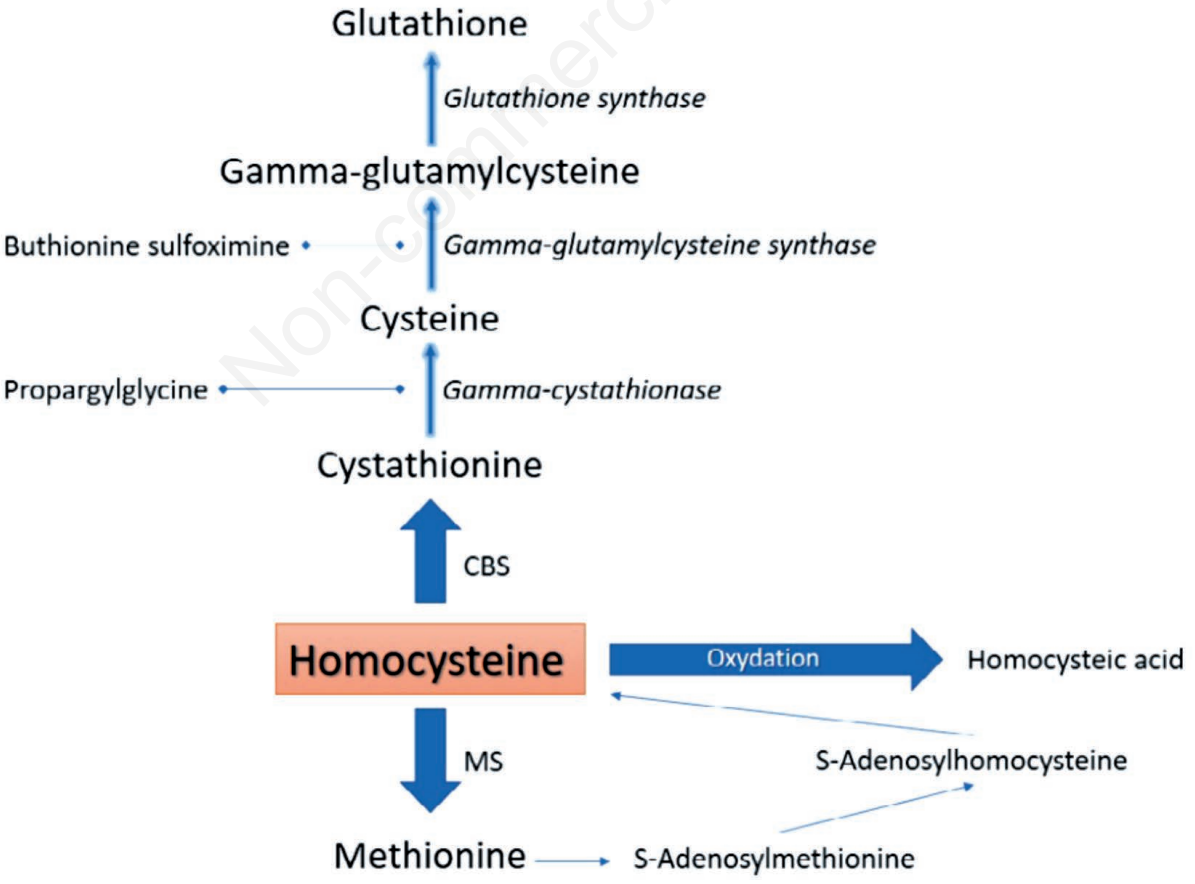

Figure 1. The transsulfuration pathway from homocysteine to glutathione (see text).

eral pathologic events induced by HHcy contributing to atherosclerosis, including endothelial dysfunction, extensive lipid deposition in the intima layer, vascular smooth muscle cell proliferation, remodeling of the extracellular matrix and immune response, increased coagulation, *etc*.[21] In addition, oxidative stress and chronic inflammation (dependent of GSH deficiency) are key factors implicated too in these events.[22] In these occurrences, NAC supplementation improves CAD, contributing to the reduction of these pathogenetic factors.[23] Concerning this, Horovitz *et al.* already demonstrated that the combination of NAC with nitroglycerin (NTG) is useful in reducing the incidence of unstable angina pectoris and its symptoms.[24]

Chronic heart failure

Heart failure is, at the moment, a worldwide cardiovascular impairment. Even through its genesis is multifactorial, elevated Hcy levels, with and without prior myocardial infarction, have a fundamental role in its occurrence and development.[25] Independently of ROS accumulation, HHcy is responsible for accumulation of interstitial and perivascular collagen (diastolic dysfunction).[26] That can also cause myocardial cell apoptosis, resulting in cardiac tissue damage, with prevalent systolic dysfunction.[27-29] Referring to the former dysfunction (that is prevalent), the association between systemic hypertension and increased Hcy plasma levels promotes a potentiation of adverse cardiac remodeling, by increasing collagen levels and coronary arteriolar wall thickening. In turn, these structural changes would result in adverse effects on cardiac function and elevated left ventricular (LV) diastolic pressure, inducing diastolic dysfunction subsequently evolving in overt diastolic heart failure.[30-32] Finally, it must also be added that NAC supplementation can attenuate cardiac fibrosis and remodeling in the setting of diastolic heart failure.[33]

Diabetic cardiomyopathy

It is another cause of morbidity and death. Results obtained in diabetic state suggest that cardiomyopathy is caused by ROS production, as a consequence of increased oxidative stress and attenuated peroxisome proliferator-activated receptor gamma. These two conditions initiate a mitochondrial lesion, favoring cardiomyopathy. In this occurrence, NAC supplementation effectively protects from cardiac disorder, possibly through the inhibition of ROS production and fibrosis.[34]

Atrial fibrillation

Several types of evidence demonstrate that this common rhythm disturbance can be related to the increased oxidative stress and chronic inflammation derived from GSH depletion and elevated Hcy is only modestly associated with an increased risk of non-valvular atrial fibrillation. Consequently, anti-oxidant drugs have tested in the prevention of this rhythm disturbance, especially rising post-operatively. Among these, N-acetylcysteine markedly reduces the incidence of post-operative atrial fibrillation possibly attenuating atrial electrophysiological remodeling.[35]

Left ventricular hypertrophy

Cellular growth and interstitial fibrosis are two leading findings of LV hypertrophy. HHcy may promote LV hypertrophy through myocardial cells growth and collagen production. But, GSH depletion favors oxidative stress and activates matrix metalloproteinase, causing endothelial dysfunction. Hypertrophy regression with acetyl-cysteine in hypertrophic cardiomyopathy (HCM) is a double-blind, randomized, placebo-controlled pilot study performed in patients with HCM. Treatment with NAC performed in these patients for 12 months reduced both cardiac hypertrophy and fibrosis.[36] In a study of Reyes *et al*. the effects of NAC were evaluated in aortic stenosis rats during the transition from LV compensate hypertrophy to overt cardiac failure. In this report also, NAC supplementation restored myocardial GSH, reducing oxidative stress. As a consequence of this, probably myocardial mitogen-activated protein kinase signaling improved and interstitial fibrosis attenuated.[37]

Neurodegenerative diseases

Apart from these positive effects on a large part of cardiovascular disorders caused by HHcy and/or GSH depletion, NAC acts on the brain too,[38] where it is able to penetrate blood-brain-barrier.[39] On cerebral neuronal cells, the supplementation, increasing the low GSH levels induced by HHcy, neutralizes ROS responsible for neurons' damage , until cells' death.[40] In addition, some researches have demonstrated that the mucolytic medication is able to limit cytokines and other inflammatory factors (TNF, interleukina-6, IK-ß) release.[40] Also the reduction of NF-k-B activity is related to the anti-inflammatory effect of NAC.

The main mechanism responsible for neurodegenerative diseases in both conditions (HHcy, and GSH deficiency) is oxidative stress. But, the insufficiency of vitamin B_6, vitamin B_{12} folic acid, antioxidants can also favor these neurodegenerations, especially in advanced age. In addition, HHcy alone can act by a neurotoxic mechanism too, by N-methyl-D-aspartate (NMDA) receptors. These induce cells apoptosis, and vascular injury. But, HHcy also promotes proliferation of smooth muscle cells, and increased burden of ischemic strokes and white matter lesions. Finally, a direct correlation between HHcy with Aß and tau levels was found in patients with Alzheimer's disease, with a significant

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deficit in memory and learning.[41] On the other hand, GSH depletion is responsible for oxidative stress and pro-inflammatory effects, damaging neuronal cells and favoring numerous mental illness. Independently of neurodegenerative diseases, both HHcy and GSH depletion may cause several neuropsychiatric sicknesses, such as schizophrenia and others, dependent from neuronal damage caused by excitotoxicity due to the hyperactivation or hypofunction of NMDA receptors located in the glutamatergic synapses.[42]

Cognitive impairment

It is known that reduced blood levels of GSH and increased Hcy plasma levels represent some important risk factors for cognitive impairment and dementia, especially in elderly subjects. Several mechanisms can explain the relationship between HHcy and cognitive impairment. Among these there are: cardiovascular disease, that represents a risk factor for dementia; silent brain infarcts cause of cognitive impairment; neuronal damage by activation of NMDA receptors; increased white matter lesions and hippocampal atrophy associated with dementia. Oxidative stress, due to the GSH depletion, is a major cause of cognitive impairment in these patients. McCaddon refers that NAC supplementation, together with B_{12} vitamin supplement, improves cognitive status in these patients. These favorable results depend on the antioxidant effect, of NAC due to increased intracellular GSH levels. The beneficial results are also facilitated by addition of vitamin B_{12} that activates the remethylation pathway.[43]

Alzheimer's disease

It is the most common form of dementia correlated with age, and consists in decline of memory, language, cognition, behavior and daily activities. Pathogenesis of this devastating disease is multifactorial. Independently of the direct, detrimental impact of HHcy on neuronal cells, diverse experiences have shown that the levels of endogenous GSH decline at an early stage of Alzheimer's disease. The consequent oxidative stress, causing protein oxidation, lipid peroxidation, DNA and RNA oxidation, as well as neurons' dysfunction, is one of the main causes of Alzheimer's disease.[44] Also the amyloid-beta peptide (Aß) formation is favored, besides HHcy, by ROS production in a vicious cycle, further making worse the disease.[45] Concerning this, some clinical trials and animal studies provided supportive evidence that NAC administration blocks the oxidative stress, showing potential effects such as possible, future medication for the disease.[46]

Parkinson disease

It is a neurodegenerative disease related to degeneration of cells involved in dopamine production. Its clinical symptoms consist in rigidity, tremor at rest and bradykinesia. But, independently of dopamine production, ageing *per se* represents an important risk factor[47] for the beginning and the progression of Parkinson's disease. The disease is also related to the reduction of antioxidant activity dependent on GSH depletion.[48] The consequent oxidative stress induces the accumulation of alfa-synucleins that plays a crucial role in Parkinson's disease. In this occurrence antioxidant compounds, as NAC, can be used to counteract oxidative stress and to protect against the programmed cells' death.[49] Nevertheless, the increased Hcy levels also have neurotoxic effects, by its direct toxic action on dopaminergic neurons and reduction of vitamins B levels. This last condition further damages neuronal cells. Finally, it must be referred that L-Dopa treatment increases total Hcy concentration, further raising its neurotoxic and excitotoxic effects.[50]

Depression of mood

It is one of the leading causes of disability worldwide. High Hcy levels cause cerebral vascular disease and neurotransmitter deficiency, one of causes responsible for depression of mood. But, reduced GSH synthesis, increasing the ROS production, also favors mood depression. In this occurrence, NAC supplementation can be useful to improve the symptomatology.[51] The drug optimizes the activity of glutamate, an excitatory amino acid neurotransmitter. In addition, it improves the oxidative activity, and reduces the inflammatory-interleukin activity. However, NAC also improves the activity of some anti-depressive drugs.[52] Mucolytic drug positively interferes with several pathological processes connected with major depressive disorders, including neuro-inflammation and glutamate neuronal activity. In addition, it positively interferes with some antidepressants, as desipramine, bupropion, escitalopram, imipramine and fluoxetine.[53]

Stroke

It is an acute event that may cause death or long-term physical disability that can depend on increased Hcy levels and/or GSH insufficiency. This cerebrovascular acute accident can be associated with various neurodegenerative diseases. Referring to GSH depletion only, both ischemic stroke and neurodegeneration can be antagonized by NAC supplementation. Specifically, NAC-intake blocks the expression of TNF-alfa and iNOS synthase, inhibiting both inflammatory and oxidative processes.[54] Biochemical damages also happening in cellular and subcellular systems, deriving from ischemia/reperfusion injuries, may be contrasted by NAC.[54,55]

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Psychiatric disorders

Psychiatric diseases, such as schizophrenia, obsessive compulsive disorders and others have a multifactorial congenital and acquired etiologies. Among these, HHcy and GSH plasma reduction are included.[56] In these cases also, the mechanisms of action are: pro-inflammatory actions, glutamatergic transmission, and oxidative stress, cells apoptosis, mitochondrial dysfunction and others.[57] For these disorders, NAC supplementation plays a role, such as adjunctive treatment to specific drugs.[58]

Conclusive remarks and future directions

Both HHcy and reduced synthesis of GSH, especially in advanced age, can be responsible for some common cerebrovascular and neurodegenerative diseases.[59] NAC, a cysteine prodrug, is able to restore the amount of intracellular GSH levels, reducing oxidative stress.[60] It might also decrease production of interleukin (IL)-1ß, that promotes atherosclerosis *via* endothelial effects on smooth muscle and foam cells.[61,62] In addition, Sekhon *et al.* observed that the treatment with NAC blocks the expression of TNF-alfa and iNOS synthase.[55] But, its administration also reduces HHcy plasma levels with multiple mechanisms.[13-16] Nevertheless, the association of the mucolytic with other drugs should be avoid in some cases. Particularly, NAC administration with NTG at the same time, even though can potentiate in-hospital prognosis of patients with unstable angina, could cause severe hypotension and/or headache.[63] In addition, the prodrug may affect the absorption of insulin in the blood stream and therefore, its administration could be avoided in diabetics treated with insulin.[64]

Conclusively, NAC supplementation is able to antagonize detrimental cardiovascular and neurodegenerative disorders rising from HHcy and/or reduced GSH. But this prodrug should be used cautiously, when contemporary given with other drugs, since it could cause some detrimental effects and/or reduce the absorption and the activity of other drugs given at same time.

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