An extensive amount of literature has been written on homocysteine (Hcy), a sulfur-containing amino acid, related to methionine metabolism [1], either degraded via the remethylation pathway or converted, via the trans-sulfuration pathway, into cysteine. Nevertheless, once more, this biochemical compound is very well represented in a laboratory, and preclinically and pathologically, but the results deriving from its correction in clinical experience are poor [2].

**Hcy and Biochemical Functions**

Hcy is related to the production of 5,10-methylenetetrahydrofolate, a fundamental step for the synthesis of thymidylate and purines and methionine, employing vitamin B12 and folate as cofactors [3–6]. The S-adenosylmethionine (SAM) to S-adenosyl-L-homocysteine (SAH) ratio defines the methylation potential of a cell [7]. If Hcy is allowed to accumulate in normal conditions, it will be rapidly metabolized to SAH [8, 9]. Whenever there is a methionine deficit, Hcy can be re-methylated to form methionine, by the employment of N5,N10-methylenetetrahydrofolate [10]. If there is an adequate amount of methionine, Hcy is employed for the production of cysteine, mediated by cystathionine-beta synthase, with pyridoxine as a cofactor [10]. Therefore, the accumulation of Hcy is dangerous when it occurs in the absence of folate as a cofactor. Recent studies are generally confident with the fact that lifestyle conditions (such as smoking, alcohol consumption, physical inactivity) may help the elevation of Hcy [11–15]. Genetic condition of hyperhomocysteinemia (HHcy) has been considered a significant risk and often fatal factor [5, 16]. Undoubtedly, the methylation reactions are strongly necessary for the brain, given that SAM is the sole donor in numerous methylation reactions, involving proteins, phospholipids, and biogenic amines [16, 17], and for packaging of many phospholipids [18]. This way, alterations of methylation with consequent Hcy accumulation lead to many congenital neural tube and central nervous system alterations [19]. The causative factors of accumulation of Hcy in healthy adult life can be diverse, due to various genetic defects or to the defects of vitamin B12 and folate [20]. A physiological increase of Hcy occurs in the brain (and CSF) and the plasma, within the aging process, and more evidently inside several neurological diseases [21].

**Hcy and Clinical Perspectives: Neurodegeneration**

It has been proven that Hcy could be linked to neurodegeneration; Hcy (in tight relationship with higher glycine levels in the brain) is an agonist of the endogenous glutamate receptors, NMDA receptors [22], influencing calcium influx [16, 23, 24], as well as through a direct activation of the group I metabotropic glutamate receptors [25]. Much evidence suggests that Hcy potentiates the toxicity of Abeta 42 deposition [26–28] and increases amyloid’s toxicity on the smooth vascular cells in the brain.
Moreover, HHcy upregulates presenilin 1, which promotes APP synthesis [30, 31]. Finally, Hcy is related to the phosphorylation process of tau. The protein phosphatase methyltransferase 1, whose methylation is SAM-dependent, regulates the activity of the protein phosphatase methyltransferase 2A, which acts as a dephosphorylating system for tau protein [32–34]. Hence, the reduced methylation capacity increases the hyperphosphorylation of tau protein, determining microtubule disaggregation, their precipitation, and the deposition of the neurofibrillary tangles.

**Hcy and Clinical Perspectives: Inflammation and Oxidative Process**

The most fascinating, irrefutable aspect of Hcy is its pro-inflammatory and pro-oxidative role. Being that the SAM-to-SAH ratio is the expression of the methylation potential of a cell, “HHcy tends to decrease the methylation potential” [10]. Therefore, Hcy can induce a global 

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lar atherosclerosis and atherothrombosis via upregulation of matrix metalloproteinases-9 (MMP-9) expression, which takes responsibility for atherosclerotic plaque instability and even their ruptures [55, 56]. Clinical trials and studies failed to demonstrate univocal and conclusive results, either preventing HHcy through the supplementation of vitamin B12, folate or both in patients or a healthy population, or considering HHcy as a real target of prevention. Much criticism may be led towards the trials implemented [15].

**Take-Home Messages**

In a debate which lasts many decades, at the moment, the only mandatory take-home messages are:

1. Hcy cannot be considered as a definite marker of vascular risk factor or neurodegeneration.
2. Hcy can be employed as a target to prevent the increase of endothelial damage and of vascular comorbidities.
3. Hcy is an inflammation marker, which seems to define adverse or poor outcomes in many clinical scenarios (sepsis, stroke, hemorrhage).
4. More studies should be done, more data should be collected, and more defined prospective population studies should be implemented, in order to finally have the solution of this enigma [57].

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**References**
