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Homocysteine and Parkinson's disease: A dangerous liaison?

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Abstract

Homocysteine, a sulphur-containing amino acid formed by demethylation of methionine, is involved in numerous processes of methyl group transfer, all playing pivotal roles in the biochemistry of the human body. Increased levels of plasma homocysteine (hyperhomocysteinemia) – which may result from a deficiency of folate, vitamin B6 or B12 or mutations in enzymes regulating the catabolism of homocysteine – are associated with a wide range of clinical manifestations, mostly affecting the central nervous system (*e.g.*, mental retardation, cerebral atrophy and epileptic seizures). Recent evidence suggests that changes in the metabolic fate of homocysteine, leading to hyperhomocysteinemia, may also play a role in the pathophysiology of neurodegenerative disorders, particularly Parkinson's disease (PD). The nervous system might be particularly sensitive to homocysteine, due to the excitotoxic-like properties of the amino acid. However, experimental findings have shown that homocysteine does not seem to posses direct, cytotoxic activity, while the amino acid has proven able to synergize with more specific neurotoxic insults. Hyperhomocysteinemia has been repeatedly reported in PD patients; the increase, however, seems mostly related to the methylated catabolism of L-Dopa, the main pharmacological treatment of PD. Therefore, hyperhomocysteinemia may not be specific to movement disorders or other neurological diseases, the condition being, in fact, rather the result of the combinations of different factors, mainly metabolic, but also genetic and pharmacological, intervening in the neurodegenerative process.

Keywords: Neurodegeneration; Movement disorders; L-Dopa; Methylation; Cytotoxicity; Folic acid; Vitamin B12

1. Homocysteine metabolism

Homocysteine (homocysteine) is a non-protein forming, sulphur-containing amino acid formed by demethylation of the essential amino acid methionine. Methionine is first adenylated to form *S*-adenosylmethionine (SAM), the direct precursor of homocysteine, through the action of the enzyme SAM synthase. SAM, which serves as methyl donor in virtually all known biological methylation reactions, is then converted into *S*-adenosylhomocysteine during such reactions (Fig 1). The hydrolysis of *S*-adenosylhomocysteine results, finally, in homocysteine. Once formed, homocysteine immediately enters a metabolic cycle consisting of two, alternative pathways aiming at either recycling or eliminating the amino acid: re-methylation or trans-sulfuration. In the re-methylation pathway, homocysteine receives a methyl group from 5-methyltetrahydrofolate, through a reaction that requires the methylcobalamin (vitamin B12)-dependent enzyme methionine synthase; in an auxiliary route, methyl groups can be transferred from choline-derived betaine. In both cases, the final result is re-conversion of homocysteine to methionine [1]. Under normal dietary conditions, half of the available homocysteine follows this pathway; appropriate levels of folate and vitamin B12 are, therefore, required to promote adequate remethylation of homocysteine, so as to regenerate methionine. In fact, a normal dietary supply of methionine does not provide all the methyl groups necessary for the many different biochemical reactions that involve a

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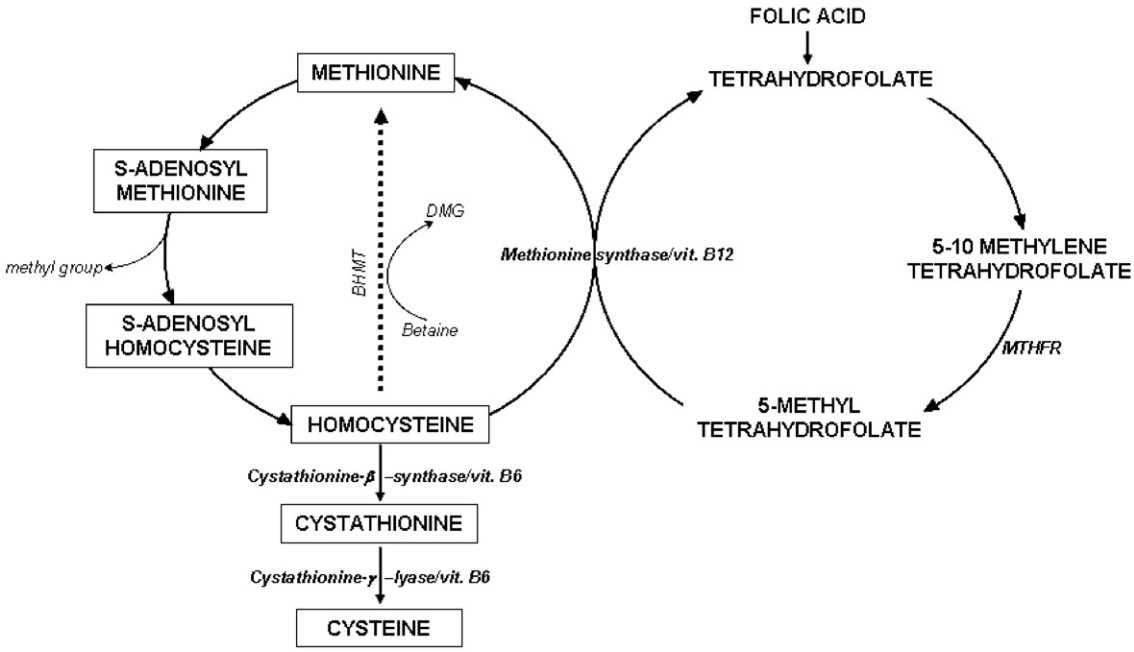

Fig. 1. Metabolic Cycle Of Homocysteine; *BHMT*: Betaine Homocysteine Methyl Transferase; *DMG*: Dymethylglycine; *MTHFR*: Methylene Tetrahydrofolate Reductase.

transmethylation process; then, additional methyl groups are generated *ex novo*, from the one-carbon folate pool [2].

In the trans-sulfuration pathway, homocysteine condenses with serine to form cystathionine, through an irreversible reaction catalyzed by the pyridoxal-5′-phosphate (vitamin B6)-dependent enzyme, cystathionine β-synthase. Finally, cystathionine is hydrolyzed to form cysteine, which may be incorporated in glutathione or excreted in the urine [1]. The equilibrium between the two catabolic pathways of homocysteine is regulated by SAM, with increased concentrations of this molecule stimulating degradation *via* the trans-sulfuration, rather than the re-methylation, pathway. A third, possible metabolic fate is represented by the export of homocysteine to the extracellular space.

Homocysteine is involved in numerous transmethylation mechanisms playing pivotal roles in the biochemistry of the human body, with SAM acting as the main donor of methyl groups in reactions targeting DNA, RNA, proteins, phospholipids and neurotransmitters [1,3].

2. Hyperhomocysteinemia

The low levels of homocysteine normally present in the plasma depend on the cellular export mechanism mentioned above, which removes excess intracellular homocysteine [4]. Homocysteine metabolism is strictly regulated, so as to maintain a balance between the re-methylation and trans-sulfuration pathways that may grant low levels of this potentially cytotoxic amino acid [5]. An abnormal increase in plasma (hyperhomocysteinemia) indicates that a defect has occurred, at a certain point, along the metabolic pathway and that the extruding mechanism is exporting the homocysteine in excess into the circulation, so as to protect the cell. This mechanism prevents toxicity to the cell but, on the other hand, exposes all tissues to the potential toxicity of hyperhomocysteinemia.

Hyperhomocysteinemia is associated with a wide range of clinical manifestations, mostly affecting the central nervous system (*e.g.*, mental retardation, cerebral atrophy and epileptic seizures) [6,7]. Hyperhomocysteinemia has also been associated with an increased risk for atherosclerotic and thrombotic vascular diseases [8–10]. Although various mechanisms have been proposed – mostly involving endothelial damage related to increased oxidative stress [11,12] – the exact cellular and molecular basis for the adverse effects of homocysteine are still elusive. Various authors have suggested that the amino acid may act as a pro-oxidant agent; indeed, the metabolism and metal-catalyzed auto-oxidation of homocysteine is paralleled by oxygen-free species formation, which may play a role in the endothelial damage associated with hyperhomocysteinemia [13–15]. *In vitro* studies have reported that homocysteine, at high concentrations, induces apoptosis (programmed cell death) in various cell lines [16–19]. This may be related, again, to the putative pro-oxidant properties of the amino acid, given the well-known role of oxidative stress as a major trigger of apoptosis [20]. The issue, however, in not completely resolved, since recent findings have questioned the actual pro-oxidant activity of homocysteine in humans [21]; analogously, we have found that incubation of isolated human lymphocytes with increasing concentrations of homocysteine do not induce significant changes in various biomarkers of oxidative stress or apoptosis [22].