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Mechanisms of homocysteine toxicity in humans

Review Article

J. Perła-Kaján[1,*], **T. Twardowski**[1], and **H. Jakubowski**[1,2]

[1] Institute of Bioorganic Chemistry, Polish Academy of Sciences, Poznań, Poland
[2] UMDNJ-New Jersey Medical School, Newark, NJ, U.S.A.

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Summary. Homocysteine, a non-protein amino acid, is an important risk factor for ischemic heart disease and stroke in humans. This review provides an overview of homocysteine influence on endothelium function as well as on protein metabolism with a special respect to posttranslational modification of protein with homocysteine thiolactone. Homocysteine is a pro-thrombotic factor, vasodilation impairing agent, pro-inflammatory factor and endoplasmatic reticulum-stress inducer. Incorporation of Hcy into protein via disulfide or amide linkages (S-homocysteinylation or N-homocysteinylation) affects protein structure and function. Protein N-homocysteinylation causes cellular toxicity and elicits autoimmune response, which may contribute to atherogenesis.

Keywords: Homocysteine – Homocysteine thiolactone – Protein N-homocysteinylation – Toxicity – Autoantibodies – Protein S-homocysteinylation

Abbreviations: APC, activated protein C; BLH, bleomycin hydrolase; ER, endoplasmatic reticulum; HDL, high density lipoprotein; HTL, homocysteine thiolactone; LDL, low density lipoprotein; MetRS, methionyl-tRNA synthetase; MS, methionine synthase; PON, paraoxonase; SAH, S-adenosylhomocysteine; SAM, S-adenosylmethionine; TPA, tissue plasminogen activator; UPR, unfolded protein response; VEGF, vascular endothelial growth factor

Introduction

Hyperhomocysteinemia has been recognized as a risk factor for a number of human diseases including cardiovascular diseases (Anderson et al., 2000; Cavalca et al., 2001; Knekt et al., 2001), stroke (Yoo and Lee, 2001), peripherial arterial occlusive disease (Kang et al., 1992) and venous thrombosis (den Heijer et al., 1996). Elevated level of homocysteine (Hcy) plays also an important role in neural tube defects (Mills et al., 1996), the development of pregnancy complications (Nelen et al., 1997) and neurodegenerative diseases (Seshadri et al., 2002). Cardiovascular diseases are a major cause of mortality in developed countries. In recent years a number of studies were undertaken to understand homocysteine metabolism and mechanisms of its toxicity. Studies that provide insight into the metabolic pathways of homocysteine, regulation strategies and negative effects of elevated level of homocysteine, are crucial for the development of a new diagnostic and therapeutic methods.

Homocysteine is involved in convertions of methionine (Met) and cysteine (Cys) (Fig. 1). The immediate precursor of homocysteine is S-adenosylhomocysteine (SAH), which is hydrolyzed by SAH hydrolase (EC 3.3.1.1) to homocysteine and adenosine. In the next step homocysteine is remethylated to methionine by methionine synthase (EC 2.1.1.13) or betaine:homocysteine methyltransferase (EC 2.1.1.5). The first step of transmethylation reactions is the activation of methionine to S-adenosylmethionine (SAM) catalyzed by methionine adenosyltransferase (EC 2.5.1.6). Methyl group of SAM is subsequently transferred onto acceptor molecule and SAH is formed.

Homocysteine enters the transsulfuration pathway and is converted into cysteine by cystathionine β-synthase (EC 4.2.1.22) and cystathionine γ-lyase (EC 4.4.1.1). The transsulfuration pathway is present only in the liver, kidney, pancreas and small intestine (Brosnan et al., 2004).

* Present address: Department of Biochemistry and Biotechnology, Agricultural University, 60637 Poznań, Poland; E-mail: asiape1@yahoo.com