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REVIEWS

Mechanisms of Toxic Effects of Homocysteine on the Nervous System

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The review describes the metabolism of homocystein, causes of hyperhomocysteinemia, mechanisms underlying the respective negative effects on the nervous system, and main principles of correction of such disorders.

Keywords: homocysteine, hyperhomocysteinemia, toxic effects, pathogenesis, nervous system.

INTRODUCTION

The role of homocysteine in neurochemical and neurophysiological processes in mammalians, including humans, is difficult to overestimate. The metabolism of homocysteine is mostly based on its re-methylation and trans-sulfonation occurring at sufficient levels of vitamins B_6, B_{12}, and that of folic acid (vitamin B_9). The balance between the above-mentioned processes crucially determines the level of homocysteine in the organism. The effects of this compound on nerve tissues in the case of its excessive amount may be due to direct neurotoxic effects or are mediated by vascular mechanisms. Homocysteine affects many physiological processes in the human organism. A high level of homocysteine causes a direct cytotoxic effect on the endothelium, which simultaneously increases the consumption of nitric oxide and initiates the release of cytokines, cyclins, and other mediators of inflammation. Also, it causes excessive proliferation of smooth muscle cells of the vascular wall and of endotheliocytes, acts as a procoagulant, increases the concentrations of low-density and very-low-density lipoproteins, and reduces the production of endothelium-derived relaxing factor and sulfated glycosaminoglycans. Thus, the role of hyperhomocysteinemia in pathological events in the vascular system is twofold. First, it damages the endothelium, which is associated with early atherogenesis, and second, it increases the probability of development of thrombosis in veins and arteries, including cerebral ones.

Metabolism of Homocysteine. Homocysteine is a low-molecular weight thiol-containing essential amino acid. It is synthesized during a multistage process of metabolism of another essential amino acid, methionine [1, 2]. The human body is not able to synthesize the latter by its own; therefore, animal food products (meat, eggs, cottage cheese) are the necessary sources of methionine [3, 4]. In the case of sufficient levels of folic acid (B_9), B_6, and B_{12} vitamins, homocysteine can be used for methionine synthesis again [5–7].

As was mentioned above, homocysteine metabolism is mainly based on two biochemical processes, re-methylation and trans-sulfonation. The balance between these processes practically determines the level of homocysteine [8]. Vitamins B_1, B_6, folic acid (B_9), and B_{12} act as coenzymes in re-methylation and trans-sulfonation [9–12]; therefore, sufficient concentrations of the above agents are necessary for the functioning of both pathways. In the first step of homocysteine biosynthesis, the adenosine group from ATP attaches to the methionine molecule, which results in the

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