Mol Cell Biochem
DOI 10.1007/s11010-013-1869-2

Nutriepigenetic regulation by folate–homocysteine–methionine axis: a review

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Received: 24 August 2013 / Accepted: 17 October 2013

Abstract Although normally folic acid is given during pregnancy, presumably to prevent neural tube defects, the mechanisms of this protection are unknown. More importantly it is unclear whether folic acid has other function during development. It is known that folic acid re-methylates homocysteine (Hcy) to methionine by methylene tetrahydrofolate reductase-dependent pathways. Folic acid also generates high-energy phosphates, behaves as an antioxidant and improves nitric oxide (NO) production by endothelial NO synthase. Interestingly, during epigenetic modification, methylation of DNA/RNA generate homocysteine unequivocally. The enhanced overexpression of methyl transferase lead to increased yield of Hcy. The accumulation of Hcy causes vascular dysfunction, reduces perfusion in the muscles thereby causing musculopathy. Another interesting fact is that children with severe hyperhomocysteinaemia (HHcy) have skeletal deformities, and do not live past teenage. HHcy is also associated with the progeria syndrome. Epilepsy is primarily caused by inhibition of gamma-amino-butyric-acid (GABA) receptor, an inhibitory neurotransmitter in the neuronal synapse. Folate deficiency leads to HHcy which then competes with GABA for binding on the GABA receptors. With so many genetic and clinical manifestations associated with folate deficiency, we propose that folate deficiency induces epigenetic alterations in the genes and thereby results in disease.

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Keywords Hyperhomocysteinaemia · Epigenetics · Neural tube defects · CNS · Chronic fatigue syndrome

Introduction

In the context of epigenetics, the importance of folate cannot be overemphasized. It is a nutritional element with vast epigenetic implications. In fact, it is the driving force behind most epigenetic mechanisms. This important molecule is easily available in nature and can be derived synthetically as well. In this review, we have focused on the clinical spectrum of its deficiency and their possible epigenetic mechanisms.

Dietary sources and metabolism

Folic acid, also known as folate or vitamin B_9 or vitamin M is a water-soluble vitamin of the B group. It comprises the aromatic pterydine ring linked to para-aminobenzoic acid and one or more glutamate residues. It is obtained from mushrooms, green leafy vegetables, spinach, yeast, grasses and fruits in our diet. It is absorbed rapidly in the upper part of the jejunum by a pH-dependent non-saturable passive diffusion process which is a high-affinity proton-coupled folate transporter (PCFT). Its bioavailability is about 78 % from natural foods and 80 % from synthetic preparations [1, 2]. Its metabolically active derivatives are methylated dihydrofolate and tetrahydrofolate—the conversion taking place in the liver after absorption from the gut (Fig. 1). Methyl tetrahydrofolate (MTHF) is delivered to cells in the circulating blood. Uptake of MTHF by the cells is mediated by four types of specific receptors in the cell walls—

Published online: 10 November 2013