TOXICOLOGY AND FORENSIC MEDICINE

Openventio PUBLISHERS

ISSN 2474-8978 Open Journal http://dx.doi.org/10.17140/TFMOJ-2-123

Commentary

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Volume 2 : Issue 2
Article Ref. #: 1000TFMOJ2123

Article History
Received: December 10th, 2017
Accepted: December 21st, 2017
Published: December 22nd, 2017

Citation
Rezk BM, Lucchesi PA. Hyperhomocysteinemia and alcoholism: A double hit? *Toxicol Forensic Med Open J*. 2017; 2(2): 84-87. doi: 10.17140/TFMOJ-2-123

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Hyperhomocysteinemia and Alcoholism: A Double Hit?

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Homocysteine (HCY) is a non-protein sulfur-containing amino acid. It has received a great deal of attention over the last two decades within the scientific community for its unique role in the induction of several diseases ranging from atherosclerotic cardiovascular disease to neural tube defects (NTD). The hypothesis that hyperhomocysteinemia (HHCY) causes atherosclerosis was proposed by McCully[1] in 1969, when he observed that children with homocysteinuria had atherosclerotic plaques of the peripheral, coronary, and cerebral vasculature. In 1976, the initial epidemiological study of Wilcken and Wilcken [2] supported this hypothesis and provided the first evidence of the pathogenic role of HCY in atherosclerotic cardiovascular disease and alcoholism. HCY strictly associated with alcohol consumption and enhanced the alcohol consumption that leads to alcohol-related disorders such as brain atrophy, epileptic seizures during withdrawal, and mood disorders.[3] Although, HHCY involves both genetic and nutritional causes,[4] the mechanism of HCY toxicity is not completely understood.

In vascular biology and under physiological conditions, the proliferation and apoptosis of cells are balanced as a symphony in which the cell death triggers cell migration and proliferation. However, in the pathogenic conditions, a selective increase in cell proliferation induces hyperplasia and a selective elevation of apoptosis leads to atrophy. As early as 1973, Ross and Glomset[5] proposed that proliferation of smooth muscle cells within the wall of the artery was the key event in the genesis of the lesions of atherosclerosis. Atherosclerosis is a multifactorial process including endothelial dysfunction, and vascular smooth muscle cells (VSMCs) apoptosis, proliferation and migration from the media to the intima, and subsequently, formation of the atherosclerotic plaques.[5-10] Indeed, apoptosis and proliferation of VSMCs are the most prominent hallmarks of atherosclerotic plaque instability. A stable atherosclerotic plaque possesses a thick fibrous cap with excessive numbers of VSMCs, whereas unstable atherosclerotic plaques have a thin fibrous cap with limited numbers of VSMCs. Apoptosis of VSMCs is substantially elevated in unstable plaques which promotes plaque rapture and subsequently led to heart attacks.[9] On the other hand, proliferation of VSMCs is associated with stable plaques.[8]

A clinical study by Guang et al[11] reported that HCY might convert a stable plaque into an unstable plaque due to the elevation of oxidative stress and chemokines in patients with acute coronary artery disease. To explain these phenomena, one possibility considered is that HCY initiates monocyte, T-lymphocyte, endothelial cell and VSMCs activities that interact with other inflammatory stimuli (such as C-reactive protein and ox-LDL), sensitize the inflammatory responsiveness leading to an enhanced production of reactive oxygen species (ROS) and a chronic inflammatory condition at the site of atherosclerotic lesions.[11] In this condition, the production of proinflammatory chemokines and ROS are enhanced further by monocyte, T-lymphocyte, endothelial cell and VSMCs.[11] These chemokines increased leukocyte adhesion and transendothelial migration.[11] At the same time, ROS induce further modified LDL into a highly oxidized form, which is taken up by macrophage and results in foam cell formation.[11] Study of Rasmussen et al[12] emphasized that HCY increased VSMC proliferation, whereas there was no change in apoptosis. Similarly, Taha et al[13] reported that HCY enhanced DNA synthesis and proliferation of VSMCs. Although the accumulation of VSMCs is the main cause of intimal thickening of vascular disease, Weissberg and co-workers[14] speculated that VSMC

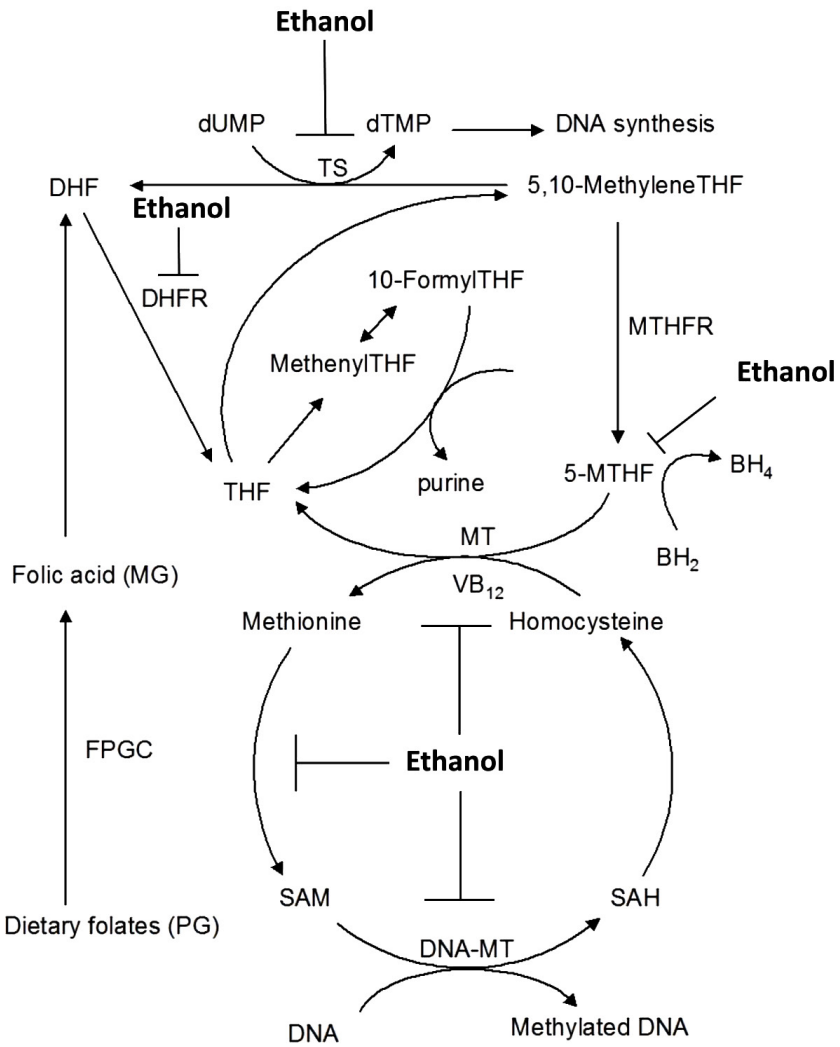
ISSN 2474-8978 http://dx.doi.org/10.17140/TFMOJ-2-123

proliferation might be beneficial. As such long-term treatment to prevent VSMCs proliferation would rupture the atherosclerotic lesions.[15] In our opinion proliferation of VSMCs is not beneficial but it might delay the rupture of the stable plaques. Importantly, a study by Buemi et al showed that HCY elevated both apoptosis and proliferation of VSMCs *in vitro*.[16] Clinically, atherosclerosis appeared to be associated with HCY levels of approximately 250 μM in hyperhomocysteinemic patients.[17-19] In addition, Yan et al[20] denoted that HCY (0.05-1 mM) elevated apoptosis of VSMCs in a dose-dependent manner. Vascular toxicity of HCY seems to be due to the elevation of oxidative stress after auto-oxidation of homocysteine into homocystine.[4] The mechanisms of induction of oxidative stress by HCY have been exclusively studied by Tyagi et al[21,22] and Moshal et al.[23]

More recent studies suggest the deleterious effects of HCY go beyond oxidative stress. For example, Kobus-Bianchini[24] reported that HCY interfered with the proliferation of neural cells and induced a decrease in neuronal differentiation in the spinal cord. Thus, the molecular networks of homocysteine are multifactorial and also include epigenetic regulation (Figure 1). Alterations in human homocysteine levels can influence DNA-methylation of specific gene sequences that may change the expression and synthesis of proteins important for the genesis and maintenance of alcohol dependence.[25,26]

The metabolism of folates and homocysteine are interrelated (Figure 1). Folic acid catalyzes methylation of homocysteine, leading to a reduction of total plasma homocysteine.[27] Conversion of homocysteine into methionine can occur in a reaction catalyzed by methionine synthetase, which uses 5-methyltetrahydrofolate (5-MTHF) as a methyl donor and cobalamin (vitamin B-12) as an essential co-factor.[28] Consumption of alcohols, negatively, interferes with the physiological and biochemical metabolic pathways of folates and homocysteine (Figure 1) that leads to a double hit. Ethanol

Figure 1: Proposed Mechanism of Interference of Ethanol with Metabolism of Folate and Homocysteine.



PG: Polyglutamate; MG: Monoglutamate; FPGC: Folylpolyglutamate carboxypeptidase; DHF: Dihydrofolate; DHFR: Dihydrofolate reductase; THF: Tetrahydrofolate; TS: Thymidylate synthetase; dUMP: Deoxyuridylate; dTMP: Thymidylate; MTHFR: Methylenetetrahydrofolate reductase; 5-MTHF: 5-methyltetrahydrofolate; MT: Methionine synthetase; VB_{12}: Vitamin B_{12}; SAM: S-adenosylmethionine; SAH: S-adenosylhomocysteine; DNA-MT: DNA methyltransferase; BH_2: dihydrobiopterin; BH_4: Tetrahydrobiopterin.[32]

ISSN 2474-8978 http://dx.doi.org/10.17140/TFMOJ-2-123

modulated liver methionine/homocysteine metabolism has been reflected by decreased SAM and increased SAH content.[29] Ethanol impaired the renal conservation of 5-methyltetrahydrofolate in the isolated perfused rat kidney.[30] Chronic alcoholism is known to interfere with one-carbon metabolism, for which folate, vitamin B-12, and vitamin B-6 serve as coenzymes.[31] Mean serum HCY was twice as high in chronic alcoholics compared to that of non-drinkers.[31]

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

REFERENCES

1. McCully KS. Vascular pathology of homocysteinemia: Implications for the pathogenesis of arteriosclerosis. *Am J Pathol*. 1969; 56: 111-128.

2. Wilcken DE, Wilcken B. The pathogenesis of coronary artery disease. A possible role for methionine metabolism. *J Clin Invest*. 1976; 57: 1079-1082. doi: 10.1172/JCI108350

3. Coppola M, Mondola R. Correlation between plasma homocysteine levels and craving in alcohol dependent stabilized patients. *Clin Nutr*. 2017. pii: S0261-5614(17)30165-6. doi: 10.1016/j.clnu.2017.05.004

4. Welch GN, Loscalzo J. Homocysteine and atherothrombosis. *N Engl J Med*. 1998; 338: 1042-1050. doi: 10.1056/NEJM199804093381507

5. Ross R, Glomset JA. Atherosclerosis and the arterial smooth muscle cell: Proliferation of smooth muscle is a key event in the genesis of the lesions of atherosclerosis. *Science*. 1973; 180: 1332-1339. doi: 10.1126/science.180.4093.1332

6. Davies MJ, Richardson PD, Woolf N, Katz DR, Mann J. Risk of thrombosis in human atherosclerotic plaques: Role of extracellular lipid, macrophage, and smooth muscle cell content. *Br Heart J*. 1993; 69: 377-381. doi: 10.1136/hrt.69.5.377

7. Ross R. Atherosclerosis--an inflammatory disease. *N Engl J Med*. 1999; 340: 115-126. doi: 10.1056/NEJM199901143400207

8. Dzau VJ, Braun-Dullaeus RC, Sedding DG. Vascular proliferation and atherosclerosis: New perspectives and therapeutic strategies. *Nat Med*. 2002; 8: 1249-1256. doi: 10.1038/nm1102-1249

9. Clarke MC, Figg N, Maguire JJ, et al. Apoptosis of vascular smooth muscle cells induces features of plaque vulnerability in atherosclerosis. *Nat Med*. 2006; 12: 1075-1080. doi: 10.1038/nm1459

10. Clarke M, Bennett M. Defining the role of vascular smooth muscle cell apoptosis in atherosclerosis. *Cell Cycle*. 2006; 5: 2329-2331. doi: 10.4161/cc.5.20.3383

11. Guang W, Jie-ming M, Xian W, Fu-chun Z. Effect of homocysteine on plaque formation and oxidative stress in patients with acute coronary syndromes. *Chinese Medical J*. 2004; 117: 1650-1654.

12. Rasmussen LM, Hansen PR, Ledet T. Homocysteine and the production of collagens, proliferation and apoptosis in human arterial smooth muscle cells. *APMIS*. 2004; 112: 598-604. doi: 10.1016/S0009-9120(03)00062-6

13. Taha S, Azzi A, Ozer NK. Homocysteine induces DNA synthesis and proliferation of vascular smooth muscle cells by a hydrogen peroxide-independent mechanism. *Antioxid Redox Signal*. 1999; 1: 365-369. doi: 10.1089/ars.1999.1.3-365

14. Weissberg PL, Clesham GJ, Bennett MR. Is vascular smooth muscle cell proliferation beneficial? *Lancet*. 1996; 347: 305-307. doi: 10.1016/S0140-6736(96)90472-9

15. Schwartz SM, Virmani R, Rosenfeld ME. The good smooth muscle cells in atherosclerosis. *Curr Atheroscler Rep*. 2000; 2: 422-429. doi: 10.1007/s11883-000-0081-5

16. Buemi M, Marino D, Di Pasquale G, et al. Effects of homocysteine on proliferation, necrosis, and apoptosis of vascular smooth muscle cells in culture and influence of folic acid. *Thromb Res*. 2001; 104: 207-213. doi: 10.1016/S0049-3848(01)00363-2

17. Clarke R, Daly L, Robinson K, et al. Hyperhomocysteinemia: An independent risk factor for vascular disease. *N Engl J Med*. 1991; 324: 1149-1155. doi: 10.1056/NEJM199104253241701

18. Malinow MR. Hyperhomocyst(e)inemia. A common and easily reversible risk factor for occlusive atherosclerosis. *Circulation*. 1990; 81: 2004-2006. doi: 10.1161/01.CIR.81.6.2004

19. Ueland PM, Refsum H. Plasma homocysteine, a risk factor for vascular disease: Plasma levels in health, disease, and drug therapy. *J Lab Clin Med*. 1989; 114: 473-501.

20. Yan SK, Chang T, Wang H, Wu L, Wang R, Meng QH. Effects of hydrogen sulfide on homocysteine-induced oxidative stress in vascular smooth muscle cells. *Biochem Biophys Res Commun*. 2006; 351: 485-491. doi: 10.1016/j.bbrc.2006.10.058

21. Tyagi N, Moshal KS, Ovechkin AV, et al. Mitochondrial mechanism of oxidative stress and systemic hypertension in hyperhomocysteinemia. *J Cell Biochem*. 2005; 96: 665-671. doi: 10.1002/jcb.20578

22. Tyagi N, Sedoris KC, Steed M, et al. Mechanisms of

ISSN 2474-8978 http://dx.doi.org/10.17140/TFMOJ-2-123

homocysteine-induced oxidative stress. *Am J Physiol Heart Circ Physiol*. 2005; 289: H2649-H2656. doi: 10.1152/ajpheart.00548.2005

23. Moshal KS, Sen U, Tyagi N, et al. Regulation of homocysteine-induced MMP-9 by ERK1/2 pathway. *Am J Physiol Cell Physiol*. 2006; 290: C883-C891. doi: 10.1152/ajpcell.00359.2005

24. Kobus-Bianchini K, Bourckhardt GF, Ammar D, Nazari EM, Müller YMR. Homocysteine-induced changes in cell proliferation and differentiation in the chick embryo spinal cord: implications for mechanisms of neural tube defects (NTD). *Reprod Toxicol.* 2017; 69: 167-173. doi: 10.1016/j.reprotox.2017.02.011

25. Bleich S, Hillemacher T. Homocysteine, alcoholism and its molecular networks. *Pharmacopsychiatry.* 2009; 42(Suppl 1): S102-S109. doi: 10.1055/s-0029-1214396

26. Kamat PK, Mallonee CJ, George AK, Tyagi SC, Tyagi N. Homocysteine, alcoholism, and its potential epigenetic mechanism. *Alcohol Clin Exp Res*. 2016; 40(12): 2474-2481. doi: 10.1111/acer.13234

27. Refsum H, Ueland PM, Nygard O, Vollset SE. Homocysteine and cardiovascular disease. *Annu Rev Med.* 1998; 49: 31-62.

28. Finkelstein JD. The metabolism of homocysteine: Pathways and regulation. *Eur J Pediatr.* 1998; 157: S40-S44. doi: 10.1007/PL00014300

29. Watson WH, Song Z, Kirpich IA, Deaciuc IV, Chen T, McClain CJ. Ethanol exposure modulates hepatic S-adenosylmethionine and S-adenosylhomocysteine levels in the isolated perfused rat liver through changes in the redox state of the NADH/NAD(+) system. *Biochim Biophys Acta.* 2011; 1812(5): 613-618. doi: 10.1016/j.bbadis.2011.01.016

30. Muldoon RT, McMartin KE. Ethanol acutely impairs the renal conservation of 5-methyltetrahydrofolate in the isolated perfused rat kidney. *Alcohol Clin Exp Re*s. 1994; 18(2): 333-339. doi: 10.1016/j.bbadis.2011.01.016

31. Cravo ML, Glória LM, Selhub J, et al. Hyperhomocysteinemia in chronic alcoholism: Correlation with folate, vitamin B-12, and vitamin B-6 status. *Am J ClinNutr.* 1996; 63(2): 220-224.

32. Rezk BM. *Antioxidants and their Metabolites: Some Toxicological Aspects*. Maastricht, Netherlands: *Universitaire Pres Maastricht;* 2004.