

Commentary

S-Adenosylhomocysteine: A Better Marker of the Development of Alzheimer's Disease than Homocysteine?

Po-Yuan Chang^a, Shao-Chun Lu^b and Chu-Huang Chen^{c,d,e,*}

^a*Department of Internal Medicine, National Taiwan University Hospital and National Taiwan University College of Medicine, Taipei, Taiwan*

^b*Department of Biochemistry and Molecular Biology, National Taiwan University College of Medicine, Taipei, Taiwan*

^c*Vascular and Medicinal Research, Texas Heart Institute at St. Luke's Episcopal Hospital, Houston, TX, USA*

^d*Department of Medicine, Baylor College of Medicine, Houston, TX, USA*

^e*Department of Medicine, China Medical University Hospital, Taichung, Taiwan*

The article by Popp and colleagues [1] highlights the association between the alteration in homocysteine metabolism and Alzheimer's disease (AD) pathology (as reflected by the cerebrospinal fluid biomarkers amyloid- β_{1-42} and P-tau181). Moreover, they raise the question as to whether *S*-adenosylhomocysteine (SAH) is a better marker of the development of AD than homocysteine. Although Popp and colleagues [1] found that phosphorylated tau was strongly associated with SAH rather than homocysteine, they did not study the mechanism underlying the SAH-AD association. The data from clinical and epidemiologic studies do not consistently show that plasma levels of homocysteine are associated with an increased risk of cognitive impairment and AD [2–4]. Similarly, clinical trials of vitamin B supplementation as a means of lowering homocysteine levels to prevent cognitive decline in AD patients have not been consistently successful [5,6]. Because

increasing evidence indicates that high plasma levels of homocysteine may not be a marker of vascular injury [6], the finding by Popp and colleagues that SAH, not homocysteine, is associated with tau accumulation in AD patients is not surprising.

Vascular injury is an essential component underlying both AD and cognitive impairment in the elderly. The relationship between hyperhomocysteinemia and vascular disease is somewhat controversial. Increasing data suggest SAH is a better indicator of cardiovascular disease and atherosclerosis than is homocysteine [7,8]. In neurodegenerative diseases, elevated homocysteine levels can lead to higher brain levels of SAH and, in turn, increase phosphorylation of tau [9], supporting the crucial role of SAH in the development of AD. Despite the strong association of increased SAH and tau in AD patients, the molecular mechanisms of SAH-induced neuronal injury (which are most likely vascular) are not clear [7,8]. We have recently studied the mechanisms involved in vascular damage induced by homocysteine and SAH [10].

In our study, exposure of human coronary artery endothelial cells to homocysteine alone, even at supra-

*Correspondence to: Chu-Huang Chen, MD, PhD, Vascular and Medicinal Research, Texas Heart Institute, 6770 Bertner Avenue, MC 2-255, Houston, TX 77030, USA. Tel.: +1 832 355 9026; E-mail: cchen@heart.thi.tmc.edu.

physiologic concentrations (500 $\mu\text{mol/L}$), did not affect cell integrity, including cell survival, cell cycle transition, and growth factor expression. However, low concentrations (25 $\mu\text{mol/L}$) of homocysteine induced cytotoxic changes in endothelial cells under culture conditions that increased the intracellular level of SAH [10]. We believe that in the absence of SAH, the vascular effects of homocysteine are negligible, even at the supra-physiologic concentrations used in many *in vitro* studies.

The critical role of SAH, rather than homocysteine, in inducing damage in vascular endothelial cells may help explain the lack of health benefits observed in several nutritional intervention trials [5], in which vitamin supplementation decreased plasma levels of homocysteine but not SAH. Unlike homocysteine, SAH levels in the plasma are not related to vitamin B6, vitamin B12, or folic acid concentrations [11,12]. Therefore, the SAH-vascular injury-AD axis may be considered one of several mechanisms linking homocysteine metabolism to the development of AD pathology [13–15]. Given the increasing evidence of the detrimental vascular effects of SAH, it would be of considerable interest to see a large-scale, prospective study of the relationship between plasma or cerebrospinal fluid levels of SAH and the development of AD.

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