The American Journal of Medicine (2005) 118, 1174-1178

ELSEVIER

THE AMERICAN JOURNAL *of* MEDICINE®

LETTERS

Folate, mitochondria, ROS, and the aging brain

To the Editor:

I read with interest the article by Kado et al.[1] They found that low folate levels are associated with cognitive decline in older adults. While reading the research literature on folate, I noticed another recently published article[2] that might have a bearing on the work of Kado et al. One may infer from it an additional mechanism by which low folate levels could cause cognitive decline.

Crott et al[2] found that folate reduced the level of 4.8 kb deletions in mitochondrial (Mt) DNA in older rats. They attributed this to folate attenuating the misincorporation of uracil into DNA, thus preventing double-strand breaks from the uracil excision process.

The 4.8 kb deletion in rats is homologous to the common 4977 bp deletion in humans.[2] There is an accumulation of the common 4977 bp deletion in the aging human brain.[3] This deletion removes 30% of the MtDNA molecule, comprising the mitochondria's respiratory capacity.[4] It also results in oxidative stress[5] from reactive oxygen species (ROS).[6]

The excess generation of ROS in the hippocampal neurons of older adults has been implicated in interfering with memory formation.[7,8] Long-term potentiation (LTP) is a form of synaptic plasticity involved in learning and memory. Excessive amounts of ROS block LTP by activating the stress-activated protein kinases JNK and p38 MAPK.

In addition, ROS have been implicated in Alzheimer's disease because they have a pro-aggregating effect on beta/A4 protein and the C-terminal fragment of amyloid precursor.[9]

This may be an additional mechanism by which low folate levels contribute to cognitive decline in older adults.

Celia M. Ross, MS
Wilmington, Del

doi:10.1016/j.amjmed.2005.03.033

References

1. Kado DM, Karlamangla AS, Huang MH, et al. Homocysteine versus the vitamins folate, B6, and B12 as predictors of cognitive function and decline in older high-functioning adults: MacArthur Studies of Successful Aging. *Am J Med*. 2005;118:161–167.
2. Crott JW, Choi SW, Branda RF, Mason JB. Accumulation of mitochondrial DNA deletions is age, tissue and folate-dependent in rats. *Mutat Res*. 2005;570:63–70.
3. Blanchard BJ, Park T, Fripp WJ, et al. A mitochondrial DNA deletion in normally aging and in Alzheimer brain tissue. *Neuroreport*. 1993;4:799–802.
4. Storm T, Rath S, Mohamed SA, et al. Mitotic brain cells are just as prone to mitochondrial deletions as neurons: a large-scale single-cell PCR study of the human caudate nucleus. *Exp Gerontol*. 2002;37:1389–1400.
5. Wei YH, Lee CF, Lee HC, et al. Increases of mitochondrial mass and mitochondrial genome in association with enhanced oxidative stress in human cells harboring 4,977 BP-deleted mitochondrial DNA. *Ann N Y Acad Sci*. 2001;928:97–112.
6. Lu CY, Lee HC, Fahn HJ, Wei YH. Oxidative damage elicited by imbalance of free radical scavenging enzymes is associated with large-scale mtDNA deletions in aging human skin. *Mutat Res*. 1999;423:11–21.
7. Knapp LT, Klann E. Role of reactive oxygen species in hippocampal long-term potentiation: contributory or inhibitory? *J Neurosci Res*. 2002;70:1–7.
8. Serrano F, Klann E. Reactive oxygen species and synaptic plasticity in the aging hippocampus. *Ageing Res Rev*. 2004;3:431–443.
9. Benzi G, Moretti A. Are reactive oxygen species involved in Alzheimer's disease? *Neurobiol Aging*. 1995;16:661–674.

The Reply:

Ms. Ross suggests an intriguing hypothesis of how low folate might contribute to cognitive decline in older persons. She speculates that low folate might lead specifically to mitochondrial DNA deletions and therefore potentiate the generation of reactive oxygen species that could ultimately result in worse cognitive function. We appreciate the interest Ms. Ross has taken in our study by suggesting this pathway. However, there is little evidence to support these speculations relative to other more plausible mechanisms such as impaired DNA methylation in the brain or cerebrovascular damage. The low folate status in our study population is far milder than the severe experimental deficiency that resulted in mitochondrial DNA damage in the study by Crott et al.[1] Furthermore, mitochondrial deletions were observed only in the liver of older rats, not in the colonic mucosa, and brain tissue was not tested. Studies in rats demonstrate that the brain is resistant to folate depletion.[2] Thus, it is unlikely that mitochondrial DNA damage would have similarly been observed in the rat brain. Clearly, the mechanisms by which low folate and/or high homocysteine

may contribute to an increased risk of cognitive decline in older persons require further investigation.

Deborah M. Kado, MD, MS
Arun S. Karlamangla, MD, PhD
Mei-Hua Huang, DrPH
Teresa E. Seeman, PhD
David Geffen School of Medicine at UCLA
Los Angeles, Calif

Jacob Selhub, PhD
Aron Troen, DPhil
Jean Mayer USDA Human Nutrition
Research Center on Aging
Tufts University
Boston, Mass

doi:10.1016/j.amjmed.2005.03.032

References

1. Crott JW, Choi SW, Branda RF, Mason JB. Accumulation of mitochondrial DNA deletions is age, tissue and folate-dependent in rats. *Mutat Res*. 2005;570:63–70.
2. Varela-Moreiras G, Selhub J. Long-term folate deficiency alters folate content and distribution differentially in rat tissues. *J Nutr*. 1992;122:986–991.

Cardiovascular abnormalities in hyperthyroidism

To the Editor:

We read with interest the study by Merce and colleagues entitled "Cardiovascular abnormalities in hyperthyroidism: a prospective Doppler echocardiographic study."[1] The study is clearly presented and covers a very important condition that is known to cause significant vascular morbidity.[2] We have previously reported excess vascular mortality in overt hyperthyroidism despite antithyroid therapy,[3] suggesting ongoing vascular risk. Merce et al conclude in their study that patients with hyperthyroidism have a high prevalence of pulmonary hypertension and atrioventricular valve regurgitation, which usually corrects after treatment of hyperthyroidism.[1] However, we would like to raise a few points regarding their study.

The study recruited a total of only 39 hyperthyroid patients and 39 age- and sex-matched controls over a 2-year period (November 1999-November 2001). No comment is made about whether the patients recruited were consecutive and unselected; also, no comment is made about the number of patients who refused to participate in the study. A total of 39 hyperthyroid patients over a 2-year period (about 20 per year) suggests that this is a highly selected cohort and may not be truly representative of the larger hyperthyroid population. This may clearly distort the findings of the study and could explain the higher prevalence of echocardiographic abnormalities demonstrated by the study.

Further evidence that the hyperthyroid cohort recruited may not be truly representative is suggested by the prevalence of atrial fibrillation reported in the study. Merce et al report an atrial fibrillation prevalence of 18% among hyperthyroid patients at recruitment. However, this prevalence is much higher than the prevalence of atrial fibrillation reported by a recent large Danish study. Frost et al reported that among 40 628 patients with hyperthyroidism, 8.3% were diagnosed as having atrial fibrillation/atrial flutter within 30 days from the date of diagnosis of hyperthyroidism;[4] this is much lower than the prevalence reported by Merce and colleagues, suggesting that patients in the latter study had a much higher prevalence of structural heart disease, even though they did exclude those with previously known cardiac or pulmonary disease. No mention is made about the possible causes of the echocardiographic abnormalities detected in hyperthyroid patients and the authors do acknowledge this in their discussion.

We congratulate the authors on attempting to study a common multi-system disorder that is increasingly being recognized to have short- and long-term consequences, especially on the cardiovascular system. Although we welcome the study findings, larger prospective controlled trials are needed to identify cardiovascular abnormalities in this cohort of patients and identification of those at particular risk of longer-term vascular morbidity and mortality.

Faizel Osman, MB, BCh, MRCP
Jayne A. Franklyn, MD, PhD, FRCP
Michael D. Gammage, MD, FRCP, FESC
Department of Cardiovascular Medicine
Department of Medicine
University Hospital Birmingham
Edgbaston, Birmingham, UK

doi:10.1016/j.amjmed.2005.02.030

References

1. Merce J, Ferras S, Olta C, et al. Cardiovascular abnormalities in hyperthyroidism: a prospective Doppler echocardiographic study. *Am J Med*. 2005;118:126–131.
2. Klein I, Ojamaa K. Thyroid hormone and the cardiovascular system. *N Engl J Med*. 2001;344:501–508.
3. Franklyn JA, Maisonneuve P, Sheppard MC, et al. Mortality after treatment of hyperthyroidism with radioactive iodine. *N Engl J Med*. 1998;338:712–718.
4. Frost L, Vestergaard P, Mosekilde L. Hyperthyrodism and risk of atrial fibrillation or flutter. A population-based study. *Arch Intern Med*. 2004;164:1675–1678.

Doctors and the drug industry: Reader feedback

To the Editor:

We read with interest the editorial[1] by Dr. Alpert in ***The American Journal of Medicine*** February 2005 issue. The