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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.

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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