Editorial

See corresponding article on page 1045.

Hippocampus as a mediator of the role of vitamin B-12 in memory

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Since the original observations of Addison in the 19th century and more recently those of Lindenbaum et al. (1), it has been known that pernicious anemia may be associated with neurological and cognitive impairments (2). It has become common practice to reassure those with serum vitamin B-12 above the traditional cutoff for pernicious anemia (148 pmol/L) that their vitamin B-12 status is "normal" and so cannot be a cause of any observed cognitive impairment. This view can no longer be supported: there is abundant evidence that those with serum vitamin B-12 concentrations in the "low-normal" range (150–300 pmol/L) may, but not necessarily will, suffer cognitive impairment that can usually be corrected by vitamin B-12 supplementation (2–4). However, it is important to use appropriate tests when assessing cognition (2), and it also appears that the association of vitamin B-12 with cognition may be context-dependent: only certain individuals will show cognitive impairment as the serum vitamin B-12 concentration declines within the normal range. The subgroups particularly susceptible to cognitive impairment with low-normal vitamin B-12 include those who carry the ε4 allele of *APOE*, are depressed, or have a very high folate status (5, 6). Other susceptible subgroups are likely; for example, it is possible that omega-3 fatty acid status influences the cognitive response to vitamin B-12 (7).

How does low-normal vitamin B-12 status cause cognitive impairment (3)? One plausible mechanism extrapolates the white matter damage in the spinal cord characteristic of vitamin B-12 deficiency to the white matter in the brain, damage to which is known to be associated with cognitive deficit. It is notable that white matter changes in the brain can be detected by MRI across the entire normal range of serum vitamin B-12, with no obvious threshold (8). Another hypothesis is that atrophy of the brain, or of specific brain regions, might mediate the cognitive effects of low-normal vitamin B-12 status. Two longitudinal community studies in elderly individuals found that the rate of whole-brain atrophy increases as serum vitamin B-12 (or holotranscobalamin) concentrations decline through the entire normal range (9, 10). There was no obvious threshold, and subjects with vitamin B-12 in the bottom tertile showed twice the rate of atrophy (1.05%/y) as those in the other tertiles (0.51%/y) (9).

In this issue of the Journal, Köbe et al. (11) describe a novel mechanism linking low-normal vitamin B-12 status with cognition: microstructural damage in subfields of the hippocampus. The authors divided subjects with mild cognitive impairment (a prodromal stage of dementia, in particular Alzheimer disease) into those with low-normal serum vitamin B-12 (153–303 pmol/L) and those with high-normal values (304–934 pmol/L). Those with low-normal vitamin B-12 performed more poorly in memory tests and showed evidence from diffusion tensor imaging by MRI of damage to the microstructure in specific regions of the hippocampus. The hippocampal subfield that was most clearly associated with low-normal vitamin B-12 status was the CA4–dentate gyrus (CA4-DG) region (**Figure 1**). Damage to microstructure of the hippocampus in MRI has previously been shown to be related to memory impairment, but this fine-structural analysis is the first to associate such subtle structural changes with vitamin B-12 status. By mediation analysis, the authors showed that this association was more than a correlation: up to 48% of the effect of low vitamin B-12 status on memory was actually mediated by the microstructural damage in the subfield CA4-DG. As can be seen from Figure 1, this subfield is only a small part of the hippocampus, which itself accounts for only ~0.5% of the volume of the whole brain. This important report will be recognized as a landmark study on nutrition and the brain.

The new study raises some important questions for science and for medicine. First, why is the microstructural damage due to low-normal vitamin B-12 status restricted mainly to the CA4-DG subfield? This subfield is a major target of the input to the hippocampus from the entorhinal cortex, via the perforant path, which carries information reaching the entorhinal cortex from many cortical regions (12). MRI studies have shown that the white matter carrying the perforant path is damaged in individuals with mild cognitive impairment and that this damage is associated with memory impairment (13). Thus, the microstructural changes in the gray matter of the hippocampal subfield CA4-DG observed by Köbe et al. could arise as a result of damage to the perforant path. The finding that this disconnection of the hippocampus from the entorhinal cortex, a characteristic feature of Alzheimer disease, may in part be determined by low vitamin B-12 status is therefore of great significance. The second scientific question is, how does low vitamin B-12 status lead to damage to the perforant path and/or to its target zone in the dentate gyrus? One possibility is that the low vitamin B-12 status leads to elevation of homocysteine, which is an established risk factor for Alzheimer disease that causes brain atrophy (reviewed in reference 14). But the authors found that the association of microstructural damage in CA4-DG with low-normal

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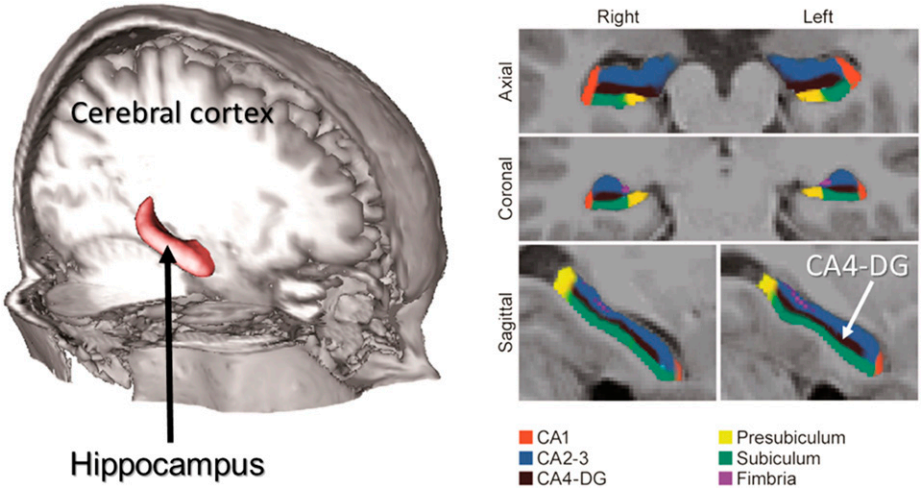

FIGURE 1 The left side of the panel shows the position of the hippocampus in the human brain. On the right, high-resolution MRI scans show the fine structure of the hippocampus in 3 orientations. The hippocampal subfields are color-coded. The subfield CA4-DG found by Köbe et al. (11) to be sensitive to vitamin B-12 status is shown in black. Reproduced from reference 12 with permission. CA4-DG, CA4–dentate gyrus.

vitamin B-12 status was still significant after adjustment for homocysteine. Another possible mechanism is related to the fact that the dentate gyrus is one of the few regions of the adult brain where neurogenesis occurs; vitamin B-12 is needed for DNA replication and so an inadequate supply could impair neurogenesis. A third alternative is impaired methylation due to insufficient vitamin B-12, leading to loss of myelin from axons of the perforant path.

A key medical question raised by the new findings is as follows: can the microstructural brain damage resulting from low vitamin B-12 status be prevented, or even reversed, by supplementing with vitamin B-12? There are several case reports that white matter damage associated with vitamin B-12 deficiency can be partially reversed by supplementation with vitamin B-12. A study that used diffusion tensor tractography in patients with vitamin B-12 deficiency found that many white matter tracts showed microstructural damage and that this could be partially reversed by administration of vitamin B-12 (15). The VITACOG (Homocysteine and B Vitamins in Cognitive Impairment) trial in persons with mild cognitive impairment found that, in those with increased plasma homocysteine, supplementation with B vitamins (folic acid, vitamins B-6 and B-12) slowed whole-brain atrophy, slowed cognitive decline, and markedly slowed the atrophy of brain regions known to be associated with Alzheimer disease, including the hippocampus (16). Bayesian network analysis in the latter study found that the main protective factor was vitamin B-12, with the following causal pathway: vitamin B-12 lowers homocysteine, which slows gray matter atrophy, which in turn slows cognitive decline. These results are consistent with the new findings and give hope that the prevention of cognitive decline due to low-normal vitamin B-12 status can be achieved by the simple step of supplementation with the vitamin. A final medical outcome of the new study is that we should no longer ignore low-normal vitamin B-12 status because long-term exposure may cause harm to the brain. As already pointed out (4), serious consideration should be given to the provision of additional vitamin B-12 to anyone whose serum vitamin B-12 is below ~300 pmol/L.

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REFERENCES

1. Lindenbaum J, Healton EB, Savage DG, Brust JC, Garrett TJ, Podell ER, Marcell PD, Stabler SP, Allen RH. Neuropsychiatric disorders caused by cobalamin deficiency in the absence of anemia or macrocytosis. N Engl J Med 1988;318:1720–8.
2. Kalita J, Misra UK. Benefit of vitamin B-12 supplementation in asymptomatic elderly: a matter of endpoints. Am J Clin Nutr 2015;102:529–30.
3. Smith AD, Refsum H. Vitamin B-12 and cognition in the elderly. Am J Clin Nutr 2009;89(Suppl):707S–11S.
4. Smith AD, Refsum H. Do we need to reconsider the desirable blood level of vitamin B12? J Intern Med 2012;271:179–82.
5. Vogiatzoglou A, Smith AD, Nurk E, Drevon CA, Ueland PM, Vollset SE, Nygaard HA, Engedal K, Tell GS, Refsum H. Cognitive function in an elderly population: interaction between vitamin B12 status, depression, and apolipoprotein E E4: the Hordaland Homocysteine Study. Psychosom Med 2013;75:20–9.
6. Selhub J, Rosenberg IH. Excessive folic acid intake and relation to adverse health outcome. Biochimie. In press.
7. Oulhaj A, Jernerén F, Refsum H, Smith AD, de Jager CA. Omega-3 fatty acid status enhances the prevention of cognitive decline by B vitamins in mild cognitive impairment. J Alzheimer's Dis 2016;50(2):547–57.
8. de Lau LM, Smith AD, Refsum H, Johnston C, Breteler MM. Plasma vitamin B12 status and cerebral white matter lesions. J Neurol Neurosurg Psychiatry 2009;80:149–57.
9. Vogiatzoglou A, Refsum H, Johnston C, Smith SM, Bradley KM, de Jager C, Budge MM, Smith AD. Vitamin B12 status and rate of brain volume loss in community-dwelling elderly. Neurology 2008;71:826–32.
10. Hooshmand B, Mangialasche F, Kalpouzos G, Solomon A, Kåreholt I, Smith AD, Refsum H, Wang R, Mühlmann M, Ertl-Wagner B, et al. Vitamin B12, folate and sulfur amino acids in relation to brain MRI measures: a longitudinal population-based study. JAMA Psychiatry. In press.
11. Köbe T, Witte AV, Schnelle A, Grittner U, Tesky VA, Pantel J, Schuchardt JP, Hahn A, Bohlken J, Rujescu D, et al. Vitamin B-12 concentration, memory performance, and hippocampal structure in patients with mild cognitive impairment. Am J Clin Nutr 2016;103:1045–54.
12. Bartsch T, Wulff P. The hippocampus in aging and disease: from plasticity to vulnerability. Neuroscience 2015;309:1–16.
13. Rogalski EJ, Murphy CM, deToledo-Morrell L, Shah RC, Moseley ME, Bammer R, Stebbins GT. Changes in parahippocampal white matter integrity in amnestic mild cognitive impairment: a diffusion tensor imaging study. Behav Neurol 2009;21:51–61.
14. Smith AD, Refsum H. Homocysteine, B vitamins and cognitive impairment. Annu Rev Nutr. In press.
15. Gupta PK, Garg RK, Gupta RK, Malhotra HS, Paliwal VK, Rathore RK, Verma R, Singh MK, Rai Y, Pandey CM. Diffusion tensor tractography and neuropsychological assessment in patients with vitamin B12 deficiency. Neuroradiology 2014;56:97–106.
16. Douaud G, Refsum H, de Jager CA, Jacoby R, Nichols TE, Smith SM, Smith AD. Preventing Alzheimer's disease-related gray matter atrophy by B-vitamin treatment. Proc Natl Acad Sci USA 2013;110:9523–8.