

Correspondence



Homocysteine and Dementia

To the Editor: Seshadri and colleagues (Feb. 14 issue)¹ report that high homocysteine levels are a risk factor for Alzheimer's disease. The effect of homocysteine on brain tissue is influenced by the absence within this tissue of two of the major metabolic routes for the elimination of homocysteine: betaine-mediated conversion and transsulfuration.^{2,3} Consequently, under conditions of folate deprivation, homocysteine can be eliminated only by export from the neuron. Increased export is problematic, however, as the authors point out, since homocysteine activates *N*-methyl-D-aspartate receptors and potentiates glutamate excitotoxicity.⁴ Minimizing homocysteine export may therefore be critical for nervous tissue, and it may be for this reason that folate is substantially more concentrated in spinal fluid than in plasma.⁵ Moreover, the decline in spinal fluid folate levels in Alzheimer's disease, but not in normal aging,⁵ may contribute to neurodegeneration. Folate levels considered adequate under normal circumstances may not be adequate in the face of a chronic degenerative condition such as Alzheimer's disease.

Studies in cultured neurons demonstrate not only that homocysteine potentiates β -amyloid-peptide neurotoxicity⁶ but also that potentiation of β -amyloid-peptide-induced neuronal apoptosis may be enhanced by homocysteine levels that are themselves benign.⁷ These findings suggest that homocysteine may have major effects on the onset and progression of neurodegeneration in Alzheimer's disease.

THOMAS B. SHEA, PH.D.

EUGENE ROGERS, PH.D.

University of Massachusetts, Lowell
Lowell, MA 01854
thomas_shea@uml.edu

1. Seshadri S, Beiser A, Selhub J, et al. Plasma homocysteine as a risk factor for dementia and Alzheimer's disease. *N Engl J Med* 2002;346:476-83.

2. Finkelstein JD. The metabolism of homocysteine: pathways and regulation. *Eur J Pediatr* 1998;157:Suppl 2:S40-S44.
3. McKeever MP, Weir DG, Molloy A, Scott JM. Betaine-homocysteine methyltransferase: organ distribution in man, pig and rat and subcellular distribution in the rat. *Clin Sci (Lond)* 1991;81:551-6.
4. Kruman II, Culmsee C, Chan SL, et al. Homocysteine elicits a DNA damage response in neurons that promotes apoptosis and hypersensitivity to excitotoxicity. *J Neurosci* 2000;20:6920-6.
5. Serot JM, Christmann D, Dubost T, Bene MC, Faure GC. CSF-folate levels are decreased in late-onset AD patients. *J Neural Transm* 2001;108:93-9.
6. White AR, Huang X, Jobling MF, et al. Homocysteine potentiates copper- and amyloid beta peptide-mediated toxicity in primary neuronal cultures: possible risk factors in the Alzheimer's-type neurodegenerative pathways. *J Neurochem* 2001;76:1509-20.
7. Ho PI, Collins SC, Dhitavat S, et al. Homocysteine potentiates amyloid beta neurotoxicity: role of oxidative stress. *J Neurochem* 2001;78:249-53.

To the Editor: In their study of plasma homocysteine as a risk factor for dementia and Alzheimer's disease, Seshadri et al. do not provide complete details about the collection of blood samples for measurement of homocysteine. The measurement of total plasma homocysteine can be done while the subject is fasting or not fasting and before or after oral methionine loading.¹ Total plasma homocysteine levels differ substantially between the fasting and nonfasting states and before and after a methionine challenge. For example, hyperhomocysteinemia after methionine loading is usually defined as a total plasma homocysteine level that is more than 2 SD above the mean.² It is usually recommended that total plasma homocysteine be measured after the subject has fasted for at least 12 hours to avoid the increases in homocysteine levels that may occur after a meal. The day-to-day variation in fasting plasma homocysteine levels is small, so it is reasonable to obtain a single measurement.³

The majority of clinical studies involving homocysteine have relied on the measurement of total plasma homocysteine during fasting.⁴ Variations in the preparation of subjects for blood-sample collection, either with respect to the rest of the study population or over time, could introduce errors and invalidate the results of analysis.

JOHANN AUER, M.D.

ROBERT BERENT, M.D.

BERND EBER, M.D.

General Hospital Wels
A-4600 Wels, Austria
johann.auer@khwels.at

INSTRUCTIONS FOR LETTERS TO THE EDITOR

Letters to the editor are considered for publication (subject to editing and abridgment) provided they do not contain material that has been submitted or published elsewhere. Please note the following: •Your letter must be typewritten and triple-spaced. •Its text, not including references, must not exceed 250 words if it is in reference to a recent *Journal* article and 400 words in all other cases (please provide a word count). •The letter must have no more than five references and one figure or table. •The letter must be signed by no more than three authors. •Letters referring to a recent *Journal* article must be received within four weeks of its publication. •Include your full mailing address, telephone number, fax number, and e-mail address. •Letters to the editor may be submitted over the Internet at <http://secure.nejm.org/letters>. You may also send us your letter by standard mail or fax.

Our address: **Letters to the Editor • New England Journal of Medicine • 10 Shattuck St. • Boston, MA 02115**

Our Web address: <http://secure.nejm.org/letters>

Our fax numbers: **617-739-9864** and **617-734-4457**

We cannot acknowledge receipt of your letter, but we will notify you when we have made a decision about publication. Rejected letters and figures will not be returned. We are unable to provide prepublication proofs. Financial associations or other possible conflicts of interest must be disclosed. Submission of a letter constitutes permission for the Massachusetts Medical Society, its licensees, and its assignees to use it in the *Journal's* various print and electronic publications and in collections, revisions, and any other form or medium.

1. Guttormsen AB, Schneede J, Fiskerstrand T, Ueland PM, Refsum HM. Plasma concentrations of homocysteine and other aminothiol compounds are related to food intake in healthy human subjects. *J Nutr* 1994;124:1934-41.
2. Dudman NP, Wilcken DE, Wang J, Lynch JF, Macey D, Lundberg P. Disordered methionine/homocysteine metabolism in premature vascular disease: its occurrence, cofactor therapy, and enzymology. *Arterioscler Thromb* 1993;13:1253-60.
3. Garg UC, Zheng ZJ, Folsom AR, et al. Short-term and long-term variability of plasma homocysteine measurement. *Clin Chem* 1997;43:141-5.
4. Auer J, Berent R, Eber B. Homocysteine: a novel risk factor in vascular disease. *Coron Health Care* 2001;5:89-99.

The authors reply:

To the Editor: Auer and colleagues express concern about the conditions of blood-sample collection. They recommend that plasma homocysteine levels be measured after an overnight fast. In our study, all the study samples were drawn in a uniform manner from subjects who were not fasting. The subjects were permitted a light breakfast or lunch. None of the samples were drawn after oral methionine loading. Several previous studies have obtained samples from nonfasting subjects.^{1,2} Thirup and Ekelund found no significant difference between the levels of plasma homocysteine measured during fasting and the postprandial levels in the same person.³

As we acknowledged in our article, the use of samples from nonfasting subjects may have "resulted in estimates of plasma homocysteine levels that were up to 20 percent higher than they would have been in fasting subjects, but any increase in the variability in plasma homocysteine values caused by this approach is likely to be random." Random variability is more likely to lead to underestimation of a true effect than to a finding of a spurious association.⁴ None of our subjects had dementia at the time that blood was drawn for plasma homocysteine measurements; hence, a systematic bias is unlikely.

We concur with Shea and Rogers that the limited capacity of the brain to metabolize homocysteine may increase its vulnerability to small elevations in plasma homocysteine. In cell cultures, homocysteine not only sensitizes hippocampal neurons to β -amyloid-peptide-induced damage; it also enhances β -amyloid-peptide generation by the induction of a stress protein located in the endoplasmic reticulum.⁵

SUDHA SESHADRI, M.D.

PHILIP A. WOLF, M.D.

Boston University School of Medicine
Boston, MA 02118
pawolf@bu.edu

1. Bots ML, Launer LJ, Lindemans J, Hofman A, Grobbee DE. Homocysteine, atherosclerosis and prevalent cardiovascular disease in the elderly: the Rotterdam Study. *J Intern Med* 1997;242:339-47.
2. Clarke R, Smith AD, Jobst KA, Refsum H, Sutton L, Ueland PM. Folate, vitamin B12, and serum total homocysteine levels in confirmed Alzheimer disease. *Arch Neurol* 1998;55:1449-55.
3. Thirup P, Ekelund S. Day-to-day, postprandial, and orthostatic variation of total plasma homocysteine. *Clin Chem* 1999;45:1280-3.
4. Clarke R, Lewington S, Donald A, et al. Underestimation of the importance of homocysteine as a risk factor for cardiovascular disease in epidemiological studies. *J Cardiovasc Risk* 2001;8:363-9.
5. Sai X, Kawamura Y, Kokame K, et al. Endoplasmic reticulum stress-inducible protein, Herp, enhances presenilin-mediated generation of amyloid beta-protein. *J Biol Chem* 2002;277:12915-20.

Leptin-Replacement Therapy in Lipodystrophy

To the Editor: Oral et al. (Feb. 21 issue)¹ demonstrate convincingly that treatment with leptin decreases triglyceride levels, improves insulin resistance, and ameliorates diabetes in patients with lipodystrophy and leptin deficiency. Minokoshi et al. have recently demonstrated that leptin can activate the enzyme AMP-activated protein kinase in skeletal muscle, thereby increasing lipid combustion and glucose uptake and establishing a molecular basis for the lipid-lowering and insulin-sensitizing effect of leptin described in this study.²

In the light of their results, Oral et al. suggest that leptin is the chief fat-derived hormone required for glucose homeostasis. Used at physiologic levels, however, leptin did not totally reverse the diabetic phenotype. Similarly, in transgenic mouse models of severe lipodystrophy, insulin resistance and diabetes are not entirely reversed by physiologic levels of leptin.³ In these models, complete reversal of the diabetic phenotype is obtained with pharmacologic levels of leptin⁴ or by fat transplantation,⁵ suggesting that in the absence of fat, leptin is not sufficient to maintain glucose and lipid homeostasis. Like leptin, adiponectin is an adipocytokine that stimulates muscle lipid oxidation and prevents liver steatosis, thereby improving sensitivity to insulin. Indeed, insulin resistance in lipodystrophic mice is completely reversed by the combination of physiologic doses of leptin and of adiponectin but is only partially reversed by either cytokine alone.⁶ Since patients with lipodystrophy and transgenic mouse models of the disorder have similar responses to treatment with leptin, it is possible that they would have similar responses to the administration of adiponectin. Determination of the adiponectin level in this subgroup of patients might be of interest for future clinical trials involving both leptin and adiponectin in patients with lipodystrophy.

FRANCK MAUVAIS-JARVIS, M.D.

Saint-Louis Hospital
75010 Paris, France
fmauvaisjarvis@aol.com

1. Oral EA, Simha V, Ruiz E, et al. Leptin-replacement therapy for lipodystrophy. *N Engl J Med* 2002;346:570-8.
2. Minokoshi Y, Kim YB, Peroni OD, et al. Leptin stimulates fatty-acid oxidation by activating AMP-activated protein kinase. *Nature* 2002;415:339-43.
3. Gavrilova O, Marcus-Samuels B, Leon LR, Vinson C, Reitman ML. Leptin and diabetes in lipodystrophic mice. *Nature* 2000;403:850-1.
4. Ebihara K, Ogawa Y, Masuzaki H, et al. Transgenic overexpression of leptin rescues insulin resistance and diabetes in a mouse model of lipodystrophic diabetes. *Diabetes* 2001;50:1440-8.
5. Gavrilova O, Marcus-Samuels B, Graham D, et al. Surgical implantation of adipose tissue reverses diabetes in lipodystrophic mice. *J Clin Invest* 2000;105:271-8.
6. Yamauchi T, Kamon J, Waki H, et al. The fat-derived hormone adiponectin reverses insulin resistance associated with both lipodystrophy and obesity. *Nat Med* 2001;7:941-6.

To the Editor: We found that when food intake was restricted in patients with lipodystrophy, elevated glucose and triglyceride levels returned to virtually normal values within days.¹ In persons who lack a storage organ for surplus calories, the result, although welcomed, was not en-