The Journal of Nutrition
Commentary

See corresponding article on page 2247.

The Effects of Iron in a Rodent Model of Alzheimer Disease

Ian J Griffin[1,2] and Christopher B Eckman[2]

[1]Department of Pediatrics, Morristown Medical Center, Morristown, NJ, USA; and [2]Biomedical Research Institute of New Jersey, Cedar Knolls, NJ, USA

In this issue of the Journal, Chen et al. (1) present data examining the effects of extremely high, nonphysiological, iron intakes in a mouse model of Alzheimer disease (AD). Outcomes include both biochemical and behavioral findings.

AD is a progressive neurodegenerative disease affecting millions of individuals. Neuropathologically, the disease is characterized by a significant loss of neurons and synapses in certain brain regions, the presence of neurofibrillary tangles made up in large part of *tau*, and an abundance of senile plaques comprised of the Alzheimer's amyloid-β peptide (Aβ). Although genetic mutations have been identified that cause the disease in a small subset of patients and multiple risk factors have been discovered (2), the majority of cases have no clear etiology. In this study, the authors seek to determine the influence of iron toxicity on the neuropathological findings in a mouse model of AD.

Nutrition has been widely considered as a modifiable risk factor for the development and progression of AD. There is evidence that diets such as the Mediterranean Diet or the Dietary Approaches to Stop Hypertension (DASH) diet can delay the onset of AD and reduce cognitive declines in patients with AD (2–4). A hybrid diet combining elements of both the Mediterranean and the DASH diets (the MIND diet—Mediterranean-DASH Intervention for Neurodegenerative Delay) may be even more effective in AD (5). For example, Morris et al. (5) followed 923 adults aged 58–98 y for a mean period of 4.5 y. The tertile with the highest adherence to the Mediterranean diet had a proportional HR for the development of AD of 0.49 (95% CI: 0.29, 0.85), the tertile with the highest adherence to the DASH diet had a proportional HR for the development of AD of 0.60 (95% CI: 0.37, 0.96), whereas for the MIND diet the value was 0.48 (95% CI: 0.29, 0.85) (5).

Several individual nutrients, including folate and vitamin A, vitamin B-12, vitamin C, and vitamin E, may be low in patients with AD (6), and a theoretical case can be made for the potential importance of many other nutrients (7), but in practice evidence for such effects is limited (2). Although some systematic reviews have found evidence that folate, vitamin E, and vitamin C (8) may have a protective effect on AD, others have not (2). Even when such effects are reported, the association with the maintenance of a "healthy dietary pattern" is of far greater importance than that with any individual nutrient (8). There is no evidence that supplementation with single nutrients has any effect on the onset or progression of AD (9).

When considering the relation between iron and AD; there is evidence that mutations in the *HFE* (hereditary hemostatic iron regulator) gene involved in iron overload (hemochromatosis) may be over-represented in adults with AD, and that these mutations increase both the risk of AD and the rate of progression of AD (10). However, in healthy adults, neither brain iron content, iron status biomarkers, nor iron intake has been shown to be associated with the onset or progression of AD, although the quality of evidence is limited (11).

Iron is known to be deposited in the brain during normal aging, as well as in a variety of neurodegenerative diseases including AD. There is some evidence that brain iron deposition may be abnormal in patients with AD, with increased iron content in a variety of brain regions including the hippocampus, parietal cortex, and putamen (12), although whether this is the cause or the consequence of neuronal damage is unclear. Chen et al., and others, have previously shown that targeted mutations in multicopper ferroxidases lead to similar brain iron deposition, oxidative damage, and behavioral abnormalities that were ameliorated by an iron chelator that was able to cross the blood–brain barrier (13).

In the current article Chen et al. (1) utilize a different approach to achieve brain iron loading: that of extremely high dietary iron intakes. When fed a diet providing 14 g Fe/kg feed (~300-fold in excess of the iron-adequate diet) for 20 wk, modest increases (2- to 2.5-fold) in brain iron or brain ferritin were seen in wild-type mice and in a mouse model of AD (the APP/PS1 mouse). This was associated with modest increases (1.3- to 3.0-fold) in Aβ and phospho-*tau*, but no significant effects on oxidative stress or on neurodevelopment were seen.

Although these results are interesting, it would be a mistake to think they have anything to tell us about the safe or desirable iron intake amounts for adult humans with AD or those at risk of AD. The high-iron mouse diet contained 300 times the amount of iron present in the iron-adequate diet. Extrapolating this to humans, a 300-fold excess over the adult DRI for iron is equal to a dietary intake of ~2.4 g/d. This daily amount is similar to the total body iron content of adults, and not very different to the amount that can produce serious acute iron toxicity in humans (60 mg/kg) (14). It represents an iron intake that could not be achieved by any conceivable dietary (food-based) means in humans, nor from any reasonable use

The authors reported no funding received for this study.
Author disclosures: IJG and CBE, no conflicts of interest.
Address correspondence to IJG (e-mail: igriffin@brinj.org).

Manuscript received July 22, 2019. Initial review completed July 26, 2019. Revision accepted July 29, 2019.
First published online August 28, 2019; doi: https://doi.org/10.1093/jn/nxz208.

of pharmacological supplements. Indeed, given the very high intakes of iron used by Chen et al. it is surprising how muted the changes are in brain iron content, which perhaps speaks to the robust mechanisms that must be present to mitigate the effects of dietary iron excess on brain iron content and neurological functioning.

Nutritional guidance for patients with AD or at risk of AD should, therefore, be the same as given to most other adults: the encouragement of a healthy balanced diet which would include diets consistent with the Mediterranean diet or the DASH diet. The study of Chen et al. provides no evidence that dietary iron is a "bad actor" in the pathogenesis of AD in humans.

Acknowledgments

Both authors read and approved the final manuscript.

References

1. Chen M, Zheng J, Liu G, Zeng C, Xu E, Zhu WZ, Anderson GJ, Chen H. High dietary iron disrupts iron homeostasis and induces amyloid-β and phospho-tau expression in the hippocampus of adult wild-type and APP/PS1 transgenic mice. J Nutr 2019; 149(12): 2267.
2. Hersi M, Irvine B, Gupta P, Gomes J, Birkett N, Krewski D. Risk factors associated with the onset and progression of Alzheimer's disease: a systematic review of the evidence. Neurotoxicology 2017;61: 143–87.
3. Solfrizzi V, Custodero C, Lozupone M, Imbimbo BP, Valiani V, Agosti P, Schilardi A, D'Introno A, La Montagna M, Calvani M, et al. Relationships of dietary patterns, foods, and micro- and macronutrients with Alzheimer's disease and late-life cognitive disorders: a systematic review. J Alzheimers Dis 2017;59:815–49.
4. van den Brink AC, Brouwer-Brolsma EM, Berendsen AAM, van de Rest O. The Mediterranean, Dietary Approaches to Stop Hypertension (DASH), and Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) diets are associated with less cognitive decline and a lower risk of Alzheimer's disease—a review. Adv Nutr 2019; 10(6):1040–60.
5. Morris MC, Tangney CC, Wang Y, Sacks FM, Bennett DA, Aggarwal NT. MIND diet associated with reduced incidence of Alzheimer's disease. Alzheimers Dement 2015;11:1007–14.
6. Lopes da Silva S, Vellas B, Elemans S, Luchsinger J, Kamphuis P, Yaffe K, Sijben J, Groenendijk M, Stijnen T. Plasma nutrient status of patients with Alzheimer's disease: systematic review and meta-analysis. Alzheimers Dement 2014;10:485–502.
7. Hu N, Yu JT, Tan L, Wang YL, Sun L, Tan L. Nutrition and the risk of Alzheimer's disease. Biomed Res Int 2013:524820.
8. Xu W, Tan L, Wang HF, Jiang T, Tan MS, Tan L, Zhao QF, Li JQ, Wang J, Yu JT. Meta-analysis of modifiable risk factors for Alzheimer's disease. J Neurol Neurosurg Psychiatry 2015;86:1299–306.
9. Muñoz Fernández SS, Ivanauskas T, Lima Ribeiro SM. Nutritional strategies in the management of Alzheimer disease: systematic review with network meta-analysis. J Am Med Dir Assoc 2017;18:897. e13–e30.
10. Nandar W, Connor JR. HFE gene variants affect iron in the brain. J Nutr 2011;141:729S–39S.
11. Hosking DE, Ayton S, Beckett N, Booth A, Peters R. More evidence is needed. Iron, incident cognitive decline and dementia: a systematic review. Ther Adv Chronic Dis 2018;9:241–56.
12. Zhu WZ, Zhong WD, Wang W, Zhan CJ, Wang CY, Qi JP, Wang JZ, Lei T. Quantitative MR phase-corrected imaging to investigate increased brain iron deposition of patients with Alzheimer disease. Radiology 2009;253:497–504.
13. Zhao L, Hadziahmetovic M, Wang C, Xu X, Song Y, Jinnah HA, Wodzinska J, Iacovelli J, Wolkow N, Krajacic P, et al. Cp/Heph mutant mice have iron-induced neurodegeneration diminished by deferiprone. J Neurochem 2015;135:958–74.
14. Liebalt EL. Acute iron poisoning [Internet]. Burns MM, Traub SJ, Wiley JF, II, editors. UpToDate [cited 2019 Jul 17]. Available from: https://www.uptodate.com/contents/acute-iron-poisoning.