ALBION®
HUMAN NUTRITION

RESEARCH NOTES

A COMPILATION OF VITAL RESEARCH UPDATES ON HUMAN NUTRITION

November, 2007 Volume 16, No. 3

Are Iron and Copper Radical Characters?

Dr. Robert DiSilvestro, Ph.D.,
Biochemistry Professor,
Human Nutrition,
The Ohio State University

In this issue of the Albion Research Notes, we have the privilege of a review article that concerns some areas of controversy in today's nutritional biochemical opinion. The guest writer for this article is Robert DiSilvestro, Professor of Nutrition at Ohio State University. Dr. DiSilvestro is the author or co-author of over 70 peer-reviewed, research publications, and he is the author of the recently published *Handbook of Minerals as Nutritional Supplements*. In addition, Dr. DiSilvestro serves as a clinical research consultant to Albion.

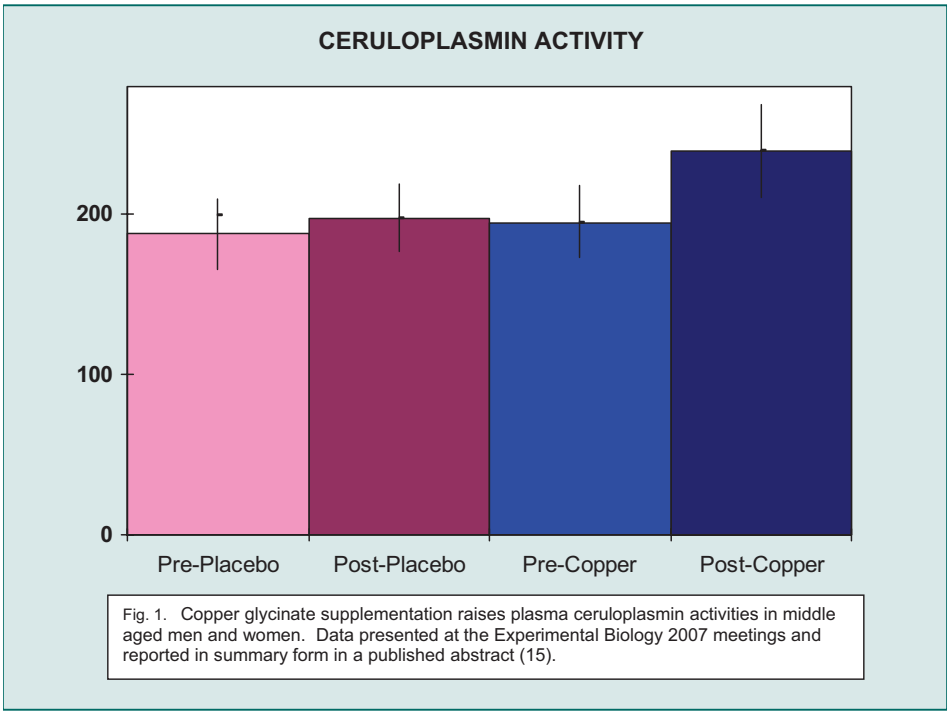

Fig. 1. Copper glycinate supplementation raises plasma ceruloplasmin activities in middle aged men and women. Data presented at the Experimental Biology 2007 meetings and reported in summary form in a published abstract (15).

Have you ever said to a person: "What I like about you is also what I don't like about you"? Well, that's what our body says to iron and copper. When these metals are harnessed in certain body molecules, the ability of iron and copper to change charges can have great function utility. On the other hand, when iron and copper are free to "roam the streets" in our body, the ability to change charges can generate free radicals. Free radicals are very reactive chemicals that cause oxidant damage, which is implicated in many health problems such as atherosclerosis, cancer, arthritis, and Alzheimer's disease. Ironically (no pun intended), the body has iron and copper containing antioxidant enzymes that actually lower the amounts of free radicals. The whole key to whether these minerals make or break free radicals is whether or not iron or copper exist in a relatively free, unbound state. In this unharnessed state, free radicals tend to be formed. In the best cases, iron and copper are held by either the molecules in which they function, or in storage proteins, or in molecules that chaperone these minerals to their functional or storage molecules.

A few scientists are calling for people, especially men, to actually make themselves somewhat iron deficient by frequently donating blood and eating as little iron as possible. However, a faulty assumption may be at work here. The assumption is that the tendency for iron to get loose and cause problems is due to eating too much iron. In reality, the tendency may be triggered by iron release rates, not the amount of iron in the body. By analogy, if a car's carburetor is flooding with gas, the solution is not to put less gas in the car. The solution is to fix the flow rate of gas into the carburetor.

Similarly, with iron, we may have to limit the flow rate out of the binding molecules. Using a more biomedical analogy, just because atherosclerotic plaques contain calcium, a low calcium diet is not advocated to prevent atherosclerosis. In support of the idea that eating more iron doesn't automatically cause more iron problems, a large survey study finds that incidence of breast cancer are not predicted by iron intake (1). Similarly, blood values for ferritin, an iron storage protein whose values rise with increased iron intake, were not related to first coronary heart disease event and time to first stroke event (2).

In contrast to the research just mentioned, two well publicized studies have found relationships for certain heart disease rates with meat iron intake, as well as with high blood ferritin (3,4). However, it is often ignored that one of the studies finds no association of risk for myocardial infarction with two other blood measures of iron status, nor with total dietary iron. It is also often ignored that in the same study, the association of myocardial infarction with serum ferritin is strongest for people with various health issues such as smoking and diabetes. Since ferritin is increased by physiological stress (5), the high ferritin values could simply be identifying people with the most physiological stress. In addition, ferritin values can sometimes be in reverse proportion to regular exercise, including just moderate exercise in middle aged or older people (*i.e.* 6).

Another issue is whether iron intake relates to colorectal cancer.

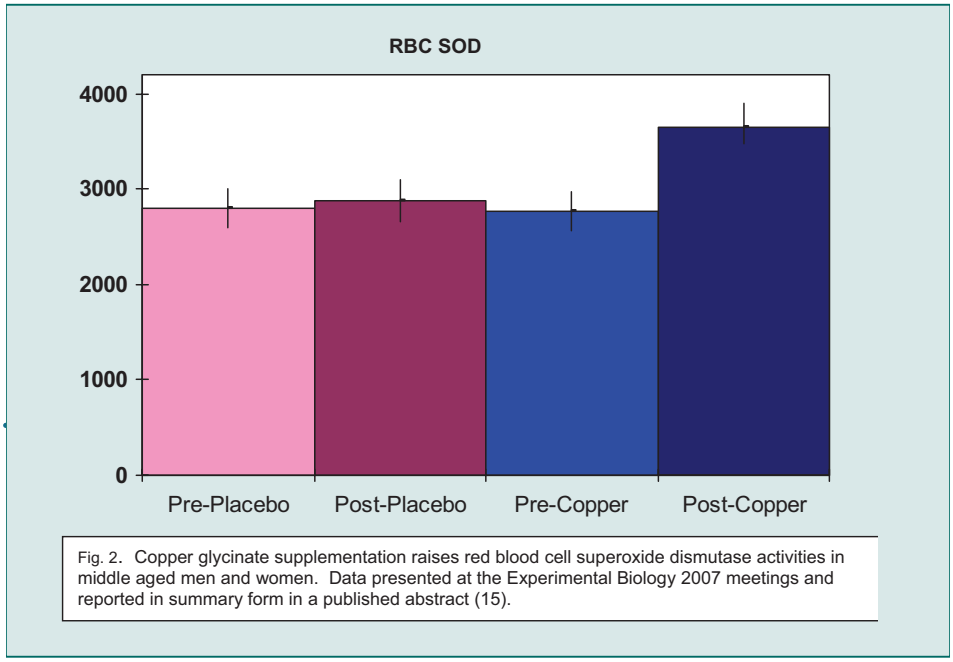

Fig. 2. Copper glycinate supplementation raises red blood cell superoxide dismutase activities in middle aged men and women. Data presented at the Experimental Biology 2007 meetings and reported in summary form in a published abstract (15).

Large surveys that compare cancer incidence to iron intake or blood markers of iron status do not give a straight answer (*i.e.* 7,8). High iron intake can appear protective, detrimental or neutral. The effect may depend on how much iron, and what particular iron complex, ends up in the colon after digestion.

Thus, these studies do not present the clear picture that is often portrayed. Although the issue is still not fully settled, there is certainly doubt that keeping iron intake low produces health benefits. On the other hand, keep iron intake to a minimal can have negative consequences. For example, a moderate iron deficiency, the kind that does not even produce anemia, can compromise immune function and induce fatigue, lethargy, and concentration problems (reviewed in 5).

If the problem with iron making radicals turns out not to revolve around iron intake, but rather iron going on the loose, how do we close the iron escape hatch? We don't fully know. One way the body slows the iron escape process is to use the other mineral on the radical producer list, namely copper. In the body, a multitasking copper enzyme called ceruloplasmin can lock blood iron onto storage and transport proteins (5). Thus, one way to keep your iron out of trouble is to eat enough copper to keep good functional ceruloplasmin levels. A recent study from our laboratory showed that in middle aged men and women, intake of Albion's copper glycinate increased ceruloplasmin activities (Figure 1). We do not know yet whether this particular increase would affect iron radical producing tendencies, but it may. Another copper enzyme, superoxide dismutase, gets rid of the radical superoxide, which can release iron from storage sites, which then causes more free radicals to be made. In the same study just noted from our laboratory, Albion's copper glycinate increased red blood cell superoxide dismutase activities (Figure 2). Another approach to limiting iron

damage may be to eat good amounts of plant flavonoids such as found in citrus fruits, green tea and soy products. Some flavonoids can prevent free iron from making free radicals in a test tube system, but this may also work in the body (9). Also, there may be some wisdom in not taking high dose iron supplements if one has no degree of iron deficiency. Although we don't know an exact safe limit for every person, it makes sense not to take many times the RDA if no known iron problem is being treated. On the other hand, a fairly high dose may often be necessary to reverse an existing iron depletion problem (5).

If copper can keep help iron out of trouble, is the cure worse than the problem? After all, copper can also make free radicals. One research group says yes; the cure is worse than the problem. They show that in a test tube setting, ceruloplasmin can lose copper atoms, which then make free radicals, which then cause oxidant damage to LDL (8). The same thing happens in a test tube if one uses free copper atoms. LDL is the carrier of the so called bad cholesterol. It is thought that oxidant damaged LDL causes atherosclerosis (hardening of the arteries). However, a number of problems exist for applying these test tube situations to real life (reviewed in 6). One, the ceruloplasmin used in the test tube studies was likely altered from normal in the preparation process. Two, in a study from our laboratory, when rats were treated to make more ceruloplasmin, they did not have more oxidant damaged LDL. Three, copper deficient rats have low ceruloplasmin and low body copper, but high rates of LDL oxidant damage (probably because copper antioxidant enzymes are low). Four, if mild copper deficiency in humans is treated with Albion's copper glycinate, LDL oxidant damage goes down, not up.

One other concern about copper causing free radical-induced oxidant damage relates to aging related loss of cognitive function, including Alzheimer's disease. In a survey of older people, those in the highest 25% of copper intake had the highest fall in cognitive functions tests after 6 years (9). However, the study details are rather odd. The authors report that in the subject subgroup with the largest cognitive decline, the high intake of copper came mostly from multi-vitamin-mineral supplements. This is strange for two reasons. One, most copper containing multi-vitamin-mineral supplements use copper oxide. Based on animal studies, very little of this type of copper gets absorbed out of the digestive system (reviewed in 5). The other strange finding is that unlike copper intake, zinc intake did not show any relationship with cognitive decline. This is perplexing since copper containing multi-vitamin-mineral supplement generally also have zinc. Therefore, if copper intake was high, so should have been zinc. Possibly, some subjects in this study took a weird copper containing supplement that also contained some toxic agent. The authors of the research article do not describe the supplements taken.

In other studies, adding copper to drinking water increases disease symptoms in a rabbit model for Alzheimer's disease (10), and in a mouse model for this disease, giving a copper binder lowers degrees of certain Alzheimer-like brain picture abnormalities (11). However, the copper binder has a lot of other actions, including making some copper functions more effective. Also, giving more copper to mice in a different Alzheimer disease model reduces symptoms (12). In another study (13), Alzheimer patients with low readings for serum copper tend to have the worst cognitive performance. Moreover, low copper enzyme readings have been found to be common in people with Alzheimer's disease (*i.e.* 14). Even so, some researchers still consider copper the bad guy because in a test tube, copper can stick to molecules that occur in Alzheimer's brains. The reasoning is that this will draw copper away from its normal binders and eventually cause free copper, which could lead to making free radicals, which can accelerate Alzheimer's disease. Unfortunately, the test tube studies never actually included the normal copper binders to see if the Alzheimer molecules could draw out the copper. Moreover, new studies say that if copper actually does stick to the Alzheimer causing molecules, copper is kicked out the brain cells, which become copper deficient (14). Therefore, Alzheimer's patients might need copper supplements to push copper back into the brain cells. In view of this possibility, a study is underway in Germany where people with Alzheimer's disease are being given copper supplements.

Therefore, the case for too much copper accelerating cognitive decline or Alzheimer's disease remains very speculative, and some evidence points

in the opposite direction (copper works against cognitive decline). In fact, most existing evidence suggests that for the general population, copper intake runs too low more often than it runs too high. For example, published studies from our laboratory and others find that many people do not eat enough copper to max out their copper enzyme readings (reviewed in 5). This type of observation is also true for our recent, not yet published research of over 200 people. This is not to say that any level of copper intake can be safe. However, based on present knowledge, copper supplementation of 2 to 3 mg per day, the common dosing range, has never been clearly shown to be harmful.

In summary, iron and copper can produce free radicals in a test tube, and some studies suggest that keeping intakes low can work against some health problems. However, closer inspection of these studies calls into question the validity of restricting iron and copper intake. Moreover, other studies blatantly contradict the concept.

References:

1. *Kabat GC, Miller AB, Jain M, Rohan TE (2007) Dietary iron and heme iron intake and risk of breast cancer: a prospective cohort study. Cancer Epidemiol Biomarkers Prev 16:1306-1308.*

2. *Knuiman MW, Divitini ML, Olynyk JK, Cullen DJ, Bartholomew HC (2003) Serum ferritin and cardiovascular disease: a 17-year follow-up study in Busselton, Western Australia. Am J Epidemiol 158:144-149.*

3. *Klipstein-Grobusch K, Grobbee DE, den Breeijen JH, Boeing H, Hofman A, Witteman JC (1999) Dietary iron and risk of myocardial infarction in the Rotterdam Study. Am. J. Epidemiol 149:421-428.*

4. *Salonen JT, Nyyssonen K, Korpela H, Tuomilehto J, Seppanen R, Salonen R (1992) High stored iron levels are associated with excess risk of myocardial infarction in eastern Finnish men. Circulation 86:803-811.*

5. *DiSilvestro RA (2005) Handbook of Minerals as Nutritional Supplements, CRC Press, Boca Raton.*

6. *Naimark BJ, Ready AE, Sawatzky JA, Boreskie S, Ducas J, Drinkwater DT, Oosterveen S (1996) Serum ferritin and heart disease: the effect of moderate exercise on stored iron levels in postmenopausal women. Can J Cardiol 12:1253-1257.*

7. *Kato I, Dnistrian AM, Schwartz M, Toniolo P, Koenig K, Shore RE, Zeleniuch JA, Akhmedkhanov A, Riboli E (1999) Iron intake, body iron stores and colorectal cancer risk in women: a nested case-control study. Int J Cancer 80:693-698.*

8. *Tseng M, Greenberg ER, Sandler RS, Baron JA, Haile RW, Blumberg BS, McGlynn KA (2000) Serum Ferritin Concentration and Recurrence of Colorectal Adenoma. Cancer Epidemiol Biomarkers Prev 9: 625-630.*

9. *DiSilvestro RA (2001) Antioxidant actions of flavonoids. In: Nutraceuticals and Functional Foods, Wildman R, ed. CRC Press, Boca Raton, FL, pp 127-142.*

10. *Sparks DL, Schreurs BG (2003) Trace Amounts of Copper in Water Induce β-Amyloid Plaques and Learning Deficits in a Rabbit Model of Alzheimer's Disease Proc Natl Acad Sci USA 100:11065-11069.*

11. *Cherny RA, Atwood CS, Xilinas, ME, Gray DN, Jones WD, McLean CA, Barnham KJ, Volitakis I, Fraser FW, Kim Y, Huang X, Goldstein LE, Moir RD, Lim JT, Beyreuther K, Zheng H, Tanzi RE, Masters CL, Bush AI (2001) Treatment with a copper-zinc chelator markedly and rapidly inhibits beta-amyloid accumulation in Alzheimer's disease transgenic mice. Neuron 30:665-676.*

12. *Bayer TA, Schäfer S, Simons A, Kemmling A, Kamer T, Tepest R, Eckert A, Schüssel K, Eikenberg O, Sturchler-Pierrat, Abramowski D, Staufenbiel M, Multhaup G (2003) Dietary Cu Stabilizes Brain Superoxide Dismutase 1 Activity and Reduces Amyloid Aβ Production in APP23 Transgenic Mice. Proc Natl Acad Sci USA 100:14187-14192.*

13. *Pajonk FG, Kessler H, Supprian T, Hamzei P, Bach D, Schweickhardt J, Herrmann W, Obeid R, Simons A, Falkai P, Multhaup G, Bayer TA (2005) Cognitive decline correlates with low plasma concentrations of copper in patients with mild to moderate Alzheimer's disease. J Alzheimer's Dis 8:23-27.*

14. *Bayer TA, Multhaup G (2005) Involvement of amyloid beta precursor protein (AbetaPP) modulated copper homeostasis in Alzheimer's disease. J Alzheimer Dis 8:201-206.*

15. *DiSilvestro RA, Jospeh E, Zhang EA, Kim YM, Sun N (2007) Copper Supplementation Effects on Erythrocyte Superoxide Dismutase Activities in Middle Aged Men and Women. FASEB J 21:A723.*

Albion Human Nutrition

100 Maple Park Blvd., Suite 110
St. Clair Shores, Michigan 48081 USA
[P] 586•774•9055 | [TF] 800•222•0733
[F] 586•774•8838
[e] info@AlbionMinerals.com