

Dietary and pharmacological factors affecting iron absorption in mice and man (Comment for a Letter to the editor)

Findings reported by Fillebeen *et al.* on the differences in heme iron absorption between mice and man underline the variation in the iron metabolic pathways involved in these two species and the extent to which they may influence iron absorption and body iron stores.¹ However, the rate of iron absorption is governed by many dietary and other factors in addition to heme iron, which according to Fillebeen *et al.* and others, is the main form of iron to be found in the meat dishes that predominate in Western diets.¹

It should be noted that the most severe pathological problems observed in relation to iron deficiency anemia are observed in the vegetarian and malnourished populations of developing countries, where heme iron absorption is not significant in comparison to other dietary forms of iron found in vegetarian meals. In these populations, the rate of iron utilization, excretion and loss appears to be higher than the rate of iron absorption from the iron forms present in vegetarian meals, resulting in a negative iron balance and iron deficiency.^{1,2}

Heme is a lipophilic protoporphyrin iron complex, similar to other lipophilic iron complexes, such as iron maltol and iron 8-hydroxyquinoline, which are more efficiently absorbed in mice, other rodents and man compared to other non-lipophilic iron formulations.^{2,5} Furthermore, it appears that the consumption of lipophilic chelators, such as 8-hydroxyquinoline can bind iron present in the diet and transport it efficiently through the gastrointestinal tract to other parts of the body.^{2,5}

In contrast to lipophilic chelator iron complexes, hydrophilic iron chelator complexes, such as those formed with deferoxamine and deferiprone, inhibit iron absorption in mice and man.^{2,4,6} Similar mechanisms apply to natural dietary chelating molecules such as phosphates and tannins, and also to hydrophilic drugs with chelating properties such as tetracyclines, all of which inhibit iron absorption in mice, other rodents and man.^{2,4,7}

Hydrophilic iron chelating drugs such as deferoxamine and deferiprone are normally used to increase iron excretion in iron overload diseases.² In this context, dietary molecules with properties similar to deferoxamine and deferiprone will not only cause a decrease in iron absorption, but also an increase in iron excretion and to an overall negative iron balance in the body iron stores, in particular, reduced iron availability to the hemopoietic tissues, leading to iron deficiency anemia.^{2,6} There are also differences between species in the route of iron excretion in addition to the differences in iron absorption observed between mice and man.^{1,2,6} For example, increased iron excretion caused by deferiprone in iron-loaded mice is mostly in the feces but in iron-loaded thalassemia patients this occurs almost exclusively in urine.^{2,6}

The metabolic route of iron absorbed from heme and other lipophilic iron chelator complexes appears to be very similar, and is mostly utilized for intracellular iron storage in ferritin and also heme production in hemopoietic cells.^{2,4,8} In the latter case, iron from heme and other lipophilic iron chelator complexes is primarily used for storage in the liver and the production of endogenous hemoglobin and myoglobin in animals and man.^{2,4,8}

Another major factor influencing the rate of iron absorption is the solubility of iron at the enterocyte site

or in other sections of the gastrointestinal tract where iron may also be absorbed under different conditions. In general, the solubility of ferric (Fe^{3+}) iron in aqueous solution at pH 7.4 is negligible (10^{-18} mol/L) and iron precipitation rapidly occurs in biological media in the absence of low molecular weight chelators or proteins with chelating properties such as transferrin. Ferrous (Fe^{2+}) iron is more soluble than ferric iron under the same conditions and is more readily absorbed. In this context, ferrous iron forms, low pH, and the presence of reducing agents such as ascorbic acid will all cause an increase in the solubility and absorption of iron from the enterocytes in comparison to ferric iron forms.^{1,2} In contrast, phosphates and other chelators causing precipitation of iron will reduce the rate of iron absorption.^{2,9}

Another major factor affecting the rate of iron absorption is the quantity of iron present in the gastrointestinal tract, in which case the amount of iron absorbed is usually proportional to the concentration of iron. For example, in Bandu siderosis, the use of iron cooking utensils led to iron overload.^{2,9} Similarly, in cases of accidental iron poisoning, large amounts of iron are rapidly absorbed causing iron-related toxic side-effects that are sometimes fatal.^{2,9,10} In these latter two conditions of increased iron absorption, the normal regulatory pathways involving ferroportin and hepcidin appear to be overwhelmed and unable to control or influence the increased rate of gastrointestinal iron absorption.^{2,9,10}

In addition to the quality and quantity of iron present in the gastrointestinal tract, many physiological changes, such as intense sporting activity, chronic disease, infections, the hematopoietic activity of the bone marrow, etc., and also the expression and activity of hepcidin, ferroportin and other regulatory molecules related to iron metabolism, also appear to influence the rate of iron absorption.^{1,2,9} In this context, further kinetic iron absorption and related metabolic studies are required to specify the rate of iron absorption from different dietary sources in normal and disease states or other non-physiological conditions, as well as in relation to the expression and activity of regulatory molecules of iron metabolism.^{1,3,9}

It is suggested that the quantity and quality of iron, including heme iron present in the gastrointestinal tract, predetermine to a great extent the level of iron absorption in mice, other animals and man, and under certain conditions the level and form of iron can bypass the iron regulatory pathways, including those of hepcidin and ferroportin.^{2,5}

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doi:10.3324/haematol.2015.138255

Key words: iron absorption, mice, men, heme, diet, pharmacological factors.

Information on authorship, contributions, and financial & other disclosures was provided by the authors and is available with the online version of this article at www.haematologica.org.

References

1. Fillebeen C, Gkouvatso K, Fragoso G, et al. Mice are poor heme absorbers and do not require intestinal Hmox1 for dietary heme iron assimilation. *Haematologica*. 2015;100(9):e334-337.
2. Kontoghiorghes GJ, Kolnagou A. Molecular factors and mechanisms affecting iron and other metal excretion or absorption in health and disease: the role of natural and synthetic chelators. *Curr Med Chem*.

- 2005;12(23):2695-2709.
3. Gasche C, Ahmad T, Tulassay Z, et al. Ferric maltol is effective in correcting iron deficiency anemia in patients with inflammatory bowel disease: results from a phase-3 clinical trial program. *Inflamm Bowel Dis.* 2015;21(3):579-588.
 4. Kontoghiorghes GJ. Chelators affecting iron absorption in mice. *Arzneimittelforschung.* 1990;40(12):1332-1335.
 5. Yamamoto RS, Williams GM, Frankel HH, Weisburger JH. 8-hydroxyquinoline: chronic toxicity and inhibitory effect on the carcinogenicity of N-2-fluorenylacetamide. *Toxicol Appl Pharmacol.* 1971;19(4):687-698.
 6. Dresow B, Fischer R, Nielsen P, Gabbe EE, Piga A. Effect of oral iron chelator L1 on iron absorption in man. *Ann NY Acad Sci.* 1998;850:466-468.
 7. Neuvonen PJ, Pentikäinen PJ, Gothoni G. Inhibition of iron absorption by tetracycline. *Br J Clin Pharmacol.* 1975;2(1):94-96.
 8. Kontoghiorghes GJ, May A. Uptake and intracellular distribution of iron from transferrin and chelators in erythroid cells. *Biol Met.* 1990;3(3-4):183-187.
 9. Finch C. Regulators of iron balance in humans. *Blood.* 1994;84(6):1697-1702.
 10. Chang TP, Rangan C. Iron poisoning: a literature-based review of epidemiology, diagnosis, and management. *Pediatr Emerg Care.* 2011;27(10):978-985.