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– Review –

Nonheme Iron Absorption and Dietary Factors

Yun-Ji Kim

Korea Food Research Institute, Kyungkido 762-420, Korea

Abstract

Iron deficiency is still a common nutritional disorder in the world. In developing countries, the bioavailability of dietary iron is often very low, mainly due to a low content of factors facilitating nonheme iron absorption. The iron content of the diet, iron status of subjects, and the actual composition of the diet are the major factors that influence the absorption of food iron. Inadequate dietary intake of iron often results from low-calorie diets, food restrictions, or single food diets. Ascorbic acid and MFP (meat, fish and poultry) are the quantitatively most important enhancers of nonheme iron absorption found in the diet. Ascorbic acid and meat have consistently been shown to enhance iron bioavailability. Major inhibitors of nonheme iron absorption are dietary fiber, phytate, and polyphenols. The availability of nonheme iron can be highly influenced by components of foods ingested concomitantly. Therefore, consumption of food in combinations can either enhance or inhibit nonheme iron absorption.

Key words : nonheme iron, iron bioavailability, iron absorption

INTRODUCTION

Iron deficiency is one of the most common nutritional problems in both developing and developed countries. Dietary iron is present in food both in inorganic forms as ferrous and ferric compounds and in organic forms, the most important of these being heme iron. Diets in developing countries usually contain negligible amounts of heme iron. Therefore, nonheme iron is the main source of dietary iron. Availability of dietary nonheme iron is affected by several enhancing and inhibiting factors present in foods.

CHEMICAL PROPERTIES OF IRON

Iron exists almost completely in some form of complex (nonionized) state in biological systems. Iron exists in two distinct oxidation states, ferrous (Fe^{2+}) and ferric (Fe^{3+}). The importance of iron as an essential element for life derives from its redox reactivity as it exists in two stable, interchangeable forms, ferrous and ferric. In a medium at a pH value slightly above 3, solubility of ferric iron decreases because the sparingly soluble ferric hydroxides are formed. The formation of sparingly soluble hydroxides and phosphates of iron in the intestinal lumen can be prevented by compounds that form complexes and/or chelates with iron[1,2]. Thermodynamically, chelates have increased solubility constants as formed with multidentate as compared with several monodentate ligands. This can be explained by the greater positive entropy change during the formation of the multidentate chelate ring. The effective stability of iron complexes can be influenced by interfering reactions in various segments of the gastrointestinal tract[1,3]. The availability of complex-bound iron depends on the effective stability of the complexes, which is related to the thermodynamic stability constant and intraluminal factors such as pH or the presence of competing metals and ligands in food. Soluble salts which remain stable through the varying conditions imposed during passage through the gastrointestinal tract, will be the most available. Iron is released from the complexes if the effective stability is low. If the effective stability

is high, absorption of iron depends on the extent to which iron is released from the intact complexes for absorption, i.e. on the physicochemical properties of the complexes. The nature of ligands that form chelate compounds with iron is an important determinant of iron absorption[4]. If the iron complex is small enough and tightly bound, it may be absorbed as an intact complex[1]. As long as ferric salts are maintained in solution, their oxidation state is not a barrier to absorption[4,5].

Solubility of iron in the intraluminal medium of the gastrointestinal tract is a prerequisite for its absorption. Several factors have been demonstrated to influence the solubility and, therefore, bioavailability of iron. These factors include pH, chemical form of iron, oxidoreductive activity of iron to form complexes, food digestibility, food processing conditions, and nutrient interactions. The amount of iron available for absorption from the diet is related to the relative concentrations of soluble iron present as ionic iron and low-molecular-weight iron complexes[6]. Low-molecular-weight complexes include soluble ferrous sulfate, ferrous fumarate, ferric citrate, sodium iron-EDTA, and iron ascorbate complexes. Insoluble and poorly available forms of iron precipitates include iron oxide, iron hydroxide and certain iron-fiber and iron-phosphoprotein complexes. When iron ions are in solution at neutral pH, the formation of insoluble hydroxides is favored with a resulting difference in the solubility of the two hydroxides formed : the solubility of ferric hydroxide at pH 7.0 is 10^{-37}M , while that of ferrous hydroxide is 10^{-15}M or approximately 10^{20} greater than that of ferric form[7]. Derman et al.[8] showed that ferric hydroxide does not readily exchange with extrinsically added iron.

IRON DEFICIENCY

Iron deficiency is one of the most prevalent nutritional disorders. According to DeMaeyer and Adiels-Tegman[9], 30% of the world population is anemic. The highest prevalence is in developing countries where the most frequent cause is poor iron bioavailability from the predominately cereal diets and blood loss due to parasitic infestation[10]. Even though iron deficiency is very low in developed countries, a significant portion of infants, adolescent girls, and pregnant women have been observed as iron deficient.

Iron deficiency can be caused by various factors. Inadequate dietary intake of iron often results from low-calorie diets, food restrictions, or single food diets. In developing countries, the bioavailability of iron from the diet is often very low, due mainly to a low content of factors facilitating nonheme iron absorption[11]. Depending on the underlying causes, iron deficiency may develop very rapidly, within a matter of weeks, or over the course of months to years. Factors associated with blood loss contribute to iron deficiency very quickly, whereas dietary deficiencies and inadequate absorption of iron affect the iron status very gradually[12]. Certain symptoms that occur in other chronic anemias are often observed in iron-deficient subjects in the absence of anemia. These include headache, fatigue, heartburn, appetite changes, vasomotor disturbances, muscular cramping, dyspnea, palpitation, menorrhagia, reduced work performance, oral cavity, and hypothermia[13-15].

IRON ABSORPTION

Digestion

It is generally agreed that only soluble iron is absorbed, and nonheme iron in food is not generally present in readily soluble forms. Nonheme iron must be released in soluble forms as a prerequisite for its bioavailability during digestion. The gastric phase of digestion and its associated acid secretion and pepsin digestion remove the inhibition to iron bioavailability by facilitating the solubilization of nonheme iron from food. Nonheme iron is apparently solubilized from its original forms in food into a common pool from which it then equilibrates with all dietary constituents to which iron can bind. The concept of all nonheme iron in diet entering the common pool has been validated by a number of studies[10,16] and appears to hold true for the nonheme iron, as present in most foods or added extrinsically as iron salts. Nonheme iron entering this

common pool can form complexes with various food constituents such as phytates, polypeptides, and fiber, or form chelates with various ligands present in food such as ascorbate, citrate, sucrose, or amino acids, or is possibly bound to components of digestive secretions such as gastrin, gastric transferrin, or mucin. Most of the components which bind iron in soluble, yet easily absorbable form have been often termed enhancers of iron absorption. Those components that bind iron in insoluble form or in soluble, but unabsorbable form have been termed inhibitors and account for much of the observed inhibition of iron bioavailability by foods.

Mechanism

Iron absorption occurs primarily in the duodenum and the most proximal part of the jejunum[17,18]. The exact mechanism which regulates the absorptive process has not been fully established. Absorption may be thought of as the sum of intestinal lumen-related effects and intestinal mucosal cellrelated effects. In other words, iron absorption is the sum of uptake and transfer[19]. The behavior of iron during digestion and absorption differs for heme and nonheme iron. Heme iron-containing proteins are digested to release the iron-porphyrin heme moiety. It has been suggested that the brush border may contain receptors for heme[20]. Heme is thought to be absorbed intact, after which the porphyrin ring is degraded and the iron presumably becomes indistinguishable from absorbed nonheme iron[21,22]. It is not clear whether uptake of inorganic iron as ferric or ferrous is via the same mechanism or by discrete mechanisms. The proposed mechanisms suggest that uptake is via the same ferrous-specific mechanisms with prerequisite reduction of ferric[23,24], or uptake of ferrous and ferric iron is by discrete mechanisms[25,26].

To be absorbed, iron must be taken up by the intestinal mucosal cell and subsequently be moved across the cell, across the serosal membrane, and to the blood, where it is picked up by transferrin. Iron-binding protein, transferrin, in the intestinal mucosa was proposed as an important mediator of intestinal iron absorption[27]. Evidence contrary to that hypothesis reviewed by Peters et al.[28]. Osterloh et al.[29] and Schumann et al.[30] have shown by immunoassays that only trace levels of transferrin exist in the gut lumen with no significant increase in situations of enhanced iron absorption. Generally, the role of transferrin appears in picking up a portion of the iron through the portal venous system and the liver, and deposits it in the bone marrow.

Nonheme iron is absorbed in experimental animals by a mechanism in which two processes operate simultaneously: the first is limited by the impermeability of the intestinal mucosa and the concentration of available iron in the lumen; whereas the second process has a rate limited capacity and displays saturation kinetics and competitive inhibition[31]. Valberg and Flànagan[3] showed that iron absorption takes place mainly by simple diffusion when iron stores are replete; whereas, binding sites are involved in the transport of iron when iron reserves are low.

Intraluminal factors

Gastrointestinal secretions play a role in altering iron absorption. Gastric acid is considered to be one of the most important luminal factors necessary for enhancing nonheme iron absorption[32]. Other components of gastric juice such as glycoproteins or unknown iron-binding substance(s) may also facilitate iron absorption. Bile enhances iron absorption because it contains significant quantities of ascorbic acid and other substances that reduce and chelate iron[33]. Pancreatic bicarbonate diminishes iron absorption, and its relative absence in cystic fibrosis and chronic pancreatitis may explain the increased iron absorption observed in these conditions[34,35]. Intestinal enzymes which release sugars and amino acids from food are believed to enhance iron absorption indirectly by forming tridentate iron chelates which remain soluble in the small intestine with a low-molecular-weight complex[36,37].

An endogenous component of gastric juice with the ability to bind iron and possibly affect the intestinal absorption of the metal has been studied by a number of workers[38~42]. Beutler et al.[43] noted that gastric juice prevented ferrous iron from precipitating at an alkaline pH. Kopke and Stewart[40] reported that gastric juice from anemic dogs enhanced the absorp-

tion of iron by healthy dogs. Although the presence of such a gastric iron-binding substance was confirmed by other workers, they were unable to verify any consistent alteration in iron-binding levels in disease states. Rudzki and Deller[44] reported that the iron binding substance was a glycoprotein containing approximately 90% of sugar residues and 10% of amino acid residues. The binding of inorganic iron by macromolecular constituents such as glycoproteins has been demonstrated *in vitro*. Although the binding is weak and probably ionic in nature[42,45], it is agreed that the complexes are not precipitated when the pH is raised. The evidences from absorption studies are conflicting. Jacobs and Owen[46] found no difference between the effects of gastric juice and HCl of similar molarity on iron absorption in achlorhydric subjects, but Jacobs and Owen[47] reported that iron absorption was potentiated significantly by gastric juice even when the effect of the acid was eliminated.

When iron was injected directly into the duodenum and jejunum, less iron was absorbed than when injected into the stomach. Bezwoda et al.[48] reported that gastric juices with pH values above 2 had a very limited capacity to solubilize the iron in bread. However, with gastric juice pH below 2, iron solubilization increased linearly with decreasing pH. They suggested that pH is the only factor in gastric juice that is of importance in modifying the absorption of nonheme iron. Barry et al.[49] reported iron absorption falls only when acid secretion is markedly reduced. Goldberg et al.[50] demonstrated that iron-deficient patients with histamine-fast achlorhydria absorbed less supplemental and dietary iron than did those with a normal acid output.

McArthur et al.[51] observed that average gastrin rise is 65~75% less and acid secretion is 30~40% less with soy than beef. This result indicates that the source of dietary protein in a meal may be an important determinant of gastric acid secretion and gastrointestinal hormone release. Potent intragastric stimulants of acid secretion act largely by stimulating release of gastrin. In dogs, cysteine, phenylalanine, and tryptophan were the most potent individual amino acids for stimulation of gastrin release[52]. In man, tryptophan and phenylalanine were the best stimulants of gastrin release and acid secretion, but cysteine was ineffective[53]. Ippoliti et al.[54] observed milk is a good stimulant of gastrin and acid in man. Saint-Hilaire et al.[55] concluded from their survey, that the component of food producing the greatest effect on the secretion of acid was protein. Since protein generally is a better buffer than is carbohydrate or fat, a correlation was sought between the acid response to the foods and their buffering capacity.

Mucosal factors

The movement of iron across the intestinal mucosa involves two major steps : 1) iron uptake from the lumen, and 2) subsequent transfer of all or a portion of this iron to the body[56,57]. When iron solutions containing iron-ascorbate complexes were placed in or perfused through duodenal loops of iron-loaded rats *in vivo*, iron uptake in the first 30 min was directly proportional to the concentration of available iron in the lumenin[31]. Radioiron placed in the duodenum of the rat was found in the carcass within 15 sec and as much as 40% of the 30 min iron uptake occurred within the first minute[58]. Starvation and the administration of endotoxin decrease the uptake of mucosal iron from the gut lumen without concomitant changes in the intestinal iron content[59,60]. Parmley et al.[61] showed that specific staining of ferric and ferrous iron in the intestinal mucosa of normal, iron-loaded, and iron-deficient animals at the ultrastructural levels has shown marked differences in the nonferritin mucosal iron content. Although it appears that the total quantity of iron in the mucosa may play a role in the absorption of iron, the amount of this iron that is bound to mucosal receptors that facilitate absorption may play a more important role[62].

Corporeal factors

Accelerated red blood cell production is related to enhanced iron absorption whether the cause be bleeding, hemolysis, or hypoxia. It is tempting to postulate that an erythrocyte-stimulating factor acts as messenger to the gut to increase iron absorption.

Most corporeal factors that alter iron absorption do not exert an effect for several days[63,64]. While corporeal factors must be the most important regulators of iron absorption, the way they inform the duodenum to transfer appropriate amounts of iron into the plasma is unknown. Hormones such as erythropoietin, thyroid, and pituitary extracts enhance iron absorption.

DIETARY FACTORS AFFECTING IRON BIOAVAILABILITY

Absorption enhancing factors

Ascorbic acid[65~68] and meat[69~71] have been consistently shown to enhance iron bioavailability. An acid environment promotes iron absorption by maintaining nonheme iron in the more soluble, ferrous form which aids in the formation of chelates. Ascorbic acid, citric acid, hydrochloric acid , and certain amino acids aid in the absorption of nonheme iron by preventing the formation of insoluble ferric hydroxide and by forming soluble complexes with ferric iron[72]. Hallberg and Rossander[73] demonstrated that a meal consumed with orange juice enhanced nonheme iron absorption by 85%. The effectiveness of ascorbic acid in enhancing iron absorption may be due to its involvement in modifying all three factors which would enhance iron absorption. Ascorbic acid lowers the food pH, reduces Fe^{3+} to Fe^{2+}, and forms a chelate which remains soluble in the alkaline environment of the small intestine with Fe^{3+} at acid pH. The promoting effect on iron absorption of ascorbic acid is dose dependent[74]. A clear dose-related effect of ascorbic acid on iron absorption was noted over 10~100mg ascorbic acid. The effect of ascorbic acid on iron absorption appeared to plateau or decrease at doses of approximately 500mg or more ascorbic acid.

The increased bioavailability of nonheme iron by animal protein has been called the meat factor effect. The enhancing effect of meat first reported by Layrisse et al.[75,76] showed that in healthy human subjects, the absorption of fortified iron added to a vegetable food was limited, reaching 0.30mg absorption with an intake of 60 mg of fortified iron. However, a supplement of 5mg iron eaten with veal muscle resulted in absorption of 0.85mg iron. Martinez-Torres and Layrisse[77] found that fish or a mixture of amino acids similar to the amino acid composition of fish increased the iron absorption from black bean from 1.4% to 2.7~3.1% in healthy human subjects. Cook and Monsen[69] have shown that all sources of animal protein are not equivalent for increasing nonheme iron absorption. Substitution of beef, lamb, pork, liver, fish, and chicken for the egg ovalbumin in a semisynthetic meal resulted in a significant 2 to 4 fold increase in iron absorption, whereas no increased iron absorption was observed with the substitution of milk, cheese, or egg. However, egg albumin, which has approximately the same amino acid composition as meat or fish, did not enhance the absorption of food iron. Gordon and Godber[70] observed that absorption of iron by rats fed diets containing beef tended to be higher, compared with animals fed diets containing lactalbumin. Worthington-Roberts et al.[78] compared the iron status of women on diets that differed by the protein sources, but were not significantly different by iron content. They found that women regularly consuming red meat had significantly better iron status as compared to women who consumed chicken and fish or milk and vegetables as the main sources of dietary protein. The importance of animal protein in iron nutrition is recognized in W HO recommendations for daily iron intake. In adult women, an intake of 28mg per day is recommended when less than 10% of the dietary energy is derived from animal protein, as compared with 14 mg per day when more than 25% of the energy is from animal protein.

Although meat enhancement of nonheme iron absorption is well documented, the mechanism(s) by which meat enhances nonheme iron absorption is controversial. To determine the mechanism of enhanced iron absorption by animal tissue protein, several investigators studied the effects of a single amino acid on iron absorption and found that histidine, lysine, and cysteine increased the absorption of ferric iron in isolated intestinal segments of rats[36]. Removal or modification of their ionizing groups (decarboxylation of histidine, removal of the epsi-

lon-amine group of lysine, and substitution of H or OH for the sulfurhydryl group of cysteine) resulted in the loss of ability of these amino acids to enhance $FeCl_3$ uptake in rats[37]. The enhancing effect of meat on iron absorption may be due to a component not related to the protein content[79]. An explanation of a mechanism to explain meat enhancement has been proposed as protein that enhances iron bioavailability by releasing peptides during digestion, which form soluble, low-molecular-weight complexes with dietary iron that readily release iron to mucosal receptors[80]. The enhancing effect of meat is most often recognized and is most pronounced in diets which are otherwise inhibitory to iron absorption[81,82].

Absorption inhibiting factors

Iron bioavailability from many plant sources is generally low. However, the factor or factors responsible for this have not been clearly identified[83]. Polyphenolic compounds, including tannins, are widely distributed in plants and thought to be the contributors that decrease in iron absorption observed when tea and coffee are consumed with various diets[84,85]. Morck et al.[67] demonstrated that tea taken with a meal reduced the absorption of iron by 64% and that coffee decreased absorption by 39%. Although coffee stimulates the secretion of gastric juices which might or supposedly enhance the iron absorption, polyphenols in coffee bind iron and offset this positive influence. Factors decreasing the iron absorption may reduce the pool of exchangeable iron by forming more insoluble or undissociated iron compounds.

Björn-Rasmussen and Hallberg[86] and Simpson et al.[87] demonstrated an inhibiting effect of cereal brans on iron absorption, likely due to content of phytate. Sodium phytate can be used experimentally as a physiological inhibitor of iron absorption. Phytates are commonly found in whole grains, bran, and soy products and decrease the bioavailability of dietary iron[88,89]. Phytates occur in a number of plants as a phosphorus storage compound. Most of the phytates are bound to cations such as potassium and magnesium. For many years, it has been assumed that phytates present in bran are the inhibiting factor, since ferric phytate complex is poorly soluble, especially at low pH ; and addition of sodium phytate markedly inhibits the iron absorption both from food iron and iron salts. However, recent findings suggest that the phytates in bran may not be the cause of the inhibitory effect[26,90].

The role of calcium and phosphate in iron absorption is controversial. Monsen and Cook[91], using an extrinsic iron-tracer technique, observed that retention of nonheme iron was impaired by 53~73% when moderate amounts of both calcium (178mg) and phosphorus (138mg) were added to the test meal, whereas iron retention was not affected by addition of an equivalent amount of either calcium or phosphate alone. On the other hand, Snedeker et al.[92] found no significant difference in iron retention from meals to which calcium, with or without phosphorus, had been added. Dawson-Hughes et al.[93] found that the addition of either calcium carbonate or hydroxyapatite significantly reduced iron retention.

Oxalates[94] and the food additive, ethylenediaminetetraacetic acid (EDTA), bind iron tightly and inhibit absorption[95]. Dietary fibers have been associated with decreased nonheme iron absorption. A slight reduction in absorption was observed with hemicellulose preparations, but pectins, guar gum, and cellulose had no effect.

SUMMARY

Iron is an essential metal for virtually all forms of living organisms. It is found in hemoglobin, myoglobin, transferrin, and enzymes. The reason that iron deficiency is still a common nutritional disorder is because the iron absorption process is affected by many factors. Those factors can be dietary, intraluminal, mucosal, and corporeal factors. Dietary factors can be classified as absorption enhancing and inhibiting factors. Enhancing factors include ascorbic acid and meat (meat factor effect). Inhibiting factors include phenolic compounds, phytate, oxalate, EDTA, and dietary fibers. Consumption of foods in combinations can either enhance or inhibit absorption. Therefore, the absolute iron content of a

diet can be less important in terms of nonheme iron bioavailability than is the composition of the diet.

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Nonheme 철분의 흡수와 식이성분

김 윤 지
한국식품개발연구원

요 약

철분 결핍은 아직도 전 세계적으로 공통적인 영양장애 중 하나이다. 특히 개발도상국에서는 식이로부터의 철분 생이용도가 매우 낮은데 이는 nonheme 철분 흡수를 매개하는 식이성분의 양이 매우 적은 것이 주 원인이다. 식이에 함유된 철분의 양, 개체의 철분 영양상태, 그리고 식이성분 등은 철분 흡수에 영향을 주는 주 요소들이다. 식이로부터 부적당한 철분의 섭취는 칼로리가 낮은 식이, 제한된 음식물 섭취, 단조로운 식이로부터 오기 쉽다. Ascorbic acid, 육류, 생선, 닭고기 등은 식이에서 nonheme 철분의 흡수를 증가시키는 매우 중요한 요소이며, ascorbic acid와 육류는 여러 연구에서 철분 생이용도 증가 효과를 일정하게 보여 주었다. Phytate, polyphenols, dietary fiber는 nonheme 철분 흡수의 주요 저해 요소로서 인지되어 왔다. 또한 nonheme 철분의 생이용도는 함께 섭취한 식품의 성분에 의해 크게 영향을 받을 수 있으므로 어떤 조합에 의한 식품의 섭취는 철분 흡수를 상승 또는 저해 시킬 수 있다.