Journal of Trace Elements in Medicine and Biology 26 (2012) 115–119

Contents lists available at SciVerse ScienceDirect

Journal of Trace Elements in Medicine and Biology

journal homepage: www.elsevier.de/jtemb

Intestinal iron absorption

Brie K. Fuqua[a,b], Christopher D. Vulpe[b], Gregory J. Anderson[a,*]

[a] Iron Metabolism Laboratory, Queensland Institute of Medical Research, Brisbane, Queensland, Australia
[b] Department of Nutrition and Toxicology, University of California, Berkeley, CA, USA

ARTICLE INFO

Article history:
Received 4 March 2012
Accepted 19 March 2012

Keywords:
Iron absorption
Iron transport
Enterocyte
Regulation
Iron overload
Iron deficiency
DMT1
FPN1
Hephaestin
Hepcidin

ABSTRACT

Intestinal iron absorption is a critical process for maintaining body iron levels within the optimal physiological range. Iron in the diet is found in a wide variety of forms, but the absorption of non-heme iron is best understood. Most of this iron is moved across the enterocyte brush border membrane by the iron transporter divalent metal-ion transporter 1, a process enhanced by the prior reduction of the iron by duodenal cytochrome B and possibly other reductases. Enterocyte iron is exported to the blood via ferroportin 1 on the basolateral membrane. This transporter acts in partnership with the ferroxidase hephaestin that oxidizes exported ferrous iron to facilitate its binding to plasma transferrin. Iron absorption is controlled by a complex network of systemic and local influences. The liver-derived peptide hepcidin binds to ferroportin, leading to its internalization and a reduction in absorption. Hepcidin expression in turn responds to body iron demands and the BMP-SMAD signaling pathway plays a key role in this process. The levels of iron and oxygen in the enterocyte also exert important influences on iron absorption. Disturbances in the regulation of iron absorption are responsible for both iron loading and iron deficiency disorders in humans.

Introduction

Under normal physiological conditions iron can only enter the human body in significant amounts from two sources: across the placenta during fetal life and across the wall of the small intestine in postnatal life. Iron intake during immediate postnatal life is quite limited and during this period the young infant relies heavily on maternally derived iron that was accumulated during the final weeks of gestation. However, this iron is utilized very rapidly in the first few months of life and thereafter iron from the diet becomes the primary source of this essential trace element for the body. The average human infant is born with around 270 mg of iron, but in the adult human body approximately 3–4 g of iron may be found [1]. All this extra iron must be derived from intestinal iron absorption. During infancy and childhood iron requirements are relatively high, but once growth declines absorption also declines to around 1 mg/day in men and 2 mg per day in women [1]. The higher average iron requirement of women reflects the need to replenish the iron lost through menstrual bleeding and pregnancies.

Although iron is essential for a myriad of body functions, it is also toxic when present in excess as the metal is able to catalyze reactions leading to the production of reactive oxygen species. This means that intestinal iron absorption must be a tightly regulated process. It must be able to provide sufficient iron for essential body functions and be able to respond relatively quickly once iron demands increase (e.g. during pregnancy), but there must also be mechanisms for limiting iron absorption once the body is iron replete. Over the last decade we have learned a great deal about how iron absorption is regulated. If this regulatory mechanism is disrupted, then significant clinical consequences can result. Perhaps the best example of this is the common primary iron loading disorder HFE-related hemochromatosis [2]. In this condition, affected individuals absorb excessive amounts of iron from their diet, despite the presence of adequate, or even increased, body iron stores. This is because mutations in the *HFE* gene lead to a defect in the mechanism by which the body responds to excess iron and which would normally limit iron absorption in an unaffected individual. The same pathway is disrupted in several other primary iron loading disorders, and also in many cases of refractory iron deficiency, albeit in this case in the opposite direction [3].

Forms of iron in the intestinal lumen

Dietary iron comes in many forms but is typically classified as either heme or non-heme iron [4]. Heme iron is found in highest abundance in meat as part of the hemoproteins hemoglobin and myoglobin. The low pH of the stomach, coupled with proteolytic enzymes in the stomach and small intestine, help to release

* Corresponding author at: Queensland Institute of Medical Research, PO Royal Brisbane Hospital, Brisbane, Queensland 4029, Australia. Tel.: +61 7 3362 0187; fax: +61 7 3362 0191.
E-mail address: greg.anderson@qimr.edu.au (G.J. Anderson).

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http://dx.doi.org/10.1016/j.jtemb.2012.03.015

heme from hemoproteins. Heme itself has very limited solubility, but it forms soluble complexes with other dietary components in the gut lumen. Iron is released from heme after it enters intestinal enterocytes.

Non-heme iron encompasses many diverse forms of iron in both plant and animal foods [4]. This iron is associated with a range of proteins, including the iron storage protein ferritin, and is also found in vacuoles in plant cells. While the low pH of the stomach can stabilize iron in the reduced Fe (II) or ferrous form, dietary iron is most often found in the oxidized Fe (III) or ferric form, which has low solubility and bioavailability. During the digestion process, however, non-heme iron likely exists in many different complexes with other digestion products in the intestinal tract, which can improve or impair absorption. For example, plant-derived phytates and tannins can sequester some forms of non-heme iron and greatly decrease their absorption, whereas ascorbic acid and compounds from meats can increase absorption [4]. The absorption of ferritin iron is not as strongly affected by iron binding components in the diet [5]. Heme iron absorption is also little affected by dietary iron chelators or enhancers [4]. Along with other evidence, this suggests that ferritin and heme iron are absorbed by different mechanisms than low molecular weight forms of iron.

Mechanism of iron passage across the enterocyte

Most iron absorption occurs in the upper part of the intestine, the duodenum and proximal jejunum, across polarized intestinal epithelial cells, or enterocytes [6]. These cells are characterized by an apical side in contact with the gut lumen and dietary contents, and a basolateral side in contact with the blood. Enterocytes emerge from dividing stem cells in the intestinal crypts and migrate up the villus, with the intestinal epithelium being completely renewed every 3–4 days. Physical properties of the gastrointestinal tract, such as the surface area of the intestine, which is increased under iron deficient conditions, and the pH in the stomach (low pH increases iron solubility), can also have an important influence on iron absorption [6].

Differentiated duodenal enterocytes express high levels of proteins involved in iron absorption from the diet. On the brush border, the major iron import protein is the ferrous iron transporter divalent metal ion transporter 1 (DMT-1) [6,7]. Mice with intestine-specific ablation of Dmt1 die shortly after birth of a severe anemia, testifying to the importance of this transporter in iron absorption [8]. A ferric reductase activity on the brush border facilitates the reduction of dietary ferric iron to the ferrous form, the substrate for DMT-1. Duodenal cytochrome B (DcytB) is able to provide some of this reductase activity, but other reductases, such as Steap2, could also play a role [9].

The absorption of heme and ferritin iron is less well understood. There is evidence that heme is taken up by receptor-mediated endocytosis [6], but a high-affinity receptor for heme in enterocytes has yet to be identified. Heme carrier protein-1/proton coupled folate transporter was identified as an apical heme transporter [6,10], however, the protein appears to play a more important role in the absorption of folate and has a much lower affinity for heme. There is some evidence that dietary ferritin is also taken into enterocytes by endocytosis [11].

Once iron has been taken up by enterocytes it can either be stored inside endogenous ferritin or exported into the blood for transport to other tissues in the body. Ingested heme iron is broken down by heme oxygenase in enterocytes to release free ferric iron, and ingested ferritin iron has also been shown to be released from ferritin [6]. Iron in a range of dietary forms ultimately ends up in the blood bound to transferrin, and it appears to enter a common cellular iron pool within enterocytes, but the nature of this pool and how iron is trafficked within the cell remain poorly understood (Fig. 1).

Ferroportin (FPN1), a multipass transmembrane protein found on the basolateral membrane of enterocytes, is the only known mammalian iron export protein and it is responsible for the movement of iron from the enterocytes into the circulation [12]. Deletion of Fpn1 in intestinal cells in mice results in a near complete block in intestinal iron absorption and a corresponding accumulation of iron in intestinal enterocytes [13]. Ferroportin likely transports iron in the ferrous form, but plasma Tf only binds iron in the ferric form, so ferroxidases are believed to play an important role in oxidizing iron transported by FPN1. Without the activity of a ferroxidase, FPN1 is internalized and degraded [14]. While other cell types in the body utilize the circulating or GPI-linked multicopper ferroxidase ceruloplasmin (CP) as a ferroxidase for FPN1, disruption of CP does not seem to affect iron absorption except under extreme situations of iron need [6]. Instead, intestinal cells utilize a membrane-bound paralog of CP called hephaestin (HP) [15]. A variety of studies have indicated that HP and FPN1 may interact [6]. Hp is mutated in the sex-linked anemia mouse, resulting in iron accumulation in intestinal enterocytes and systemic anemia [15]. Amyloid precursor protein (APP) is another ferroxidase that is expressed in intestinal enterocytes that could potentially play a role in intestinal iron absorption [16].

Regulation of iron absorption

There are no regulated mechanisms known for the removal of iron from the body, and thus it is critical that iron absorption is tightly regulated to precisely match body iron requirements. In a healthy adult, most of the body's daily iron needs are met by the recycling of iron from senescent red blood cells by reticuloendothelial macrophages. However, the body must absorb sufficient iron from the diet to make up for obligate losses due to the shedding of epithelial cells, menstruation, and several other minor sources. Iron supply also needs to respond to the increased requirements of growth, pregnancy, hypoxic conditions, and after blood loss. If too much iron is absorbed, as in genetic diseases like hemochromatosis, iron will eventually overwhelm the storage capacity of the body, resulting in iron-mediated oxidative damage in tissues, and potentially organ disease and failure. The regulation of iron absorption is mediated through the complex interaction of systemic and local influences.

Systemic regulation

The absorption of iron from intestinal enterocytes, as well as the efflux of recycled iron from macrophages, is systemically controlled by the 25 amino acid peptide hormone hepcidin [17,18]. Hepcidin, which is primarily produced by hepatocytes in the liver, circulates in the blood and binds to the iron exporter FPN1 on cell surfaces, including the enterocyte basolateral membrane. This binding leads to the internalization and degradation of FPN1, and thus iron release into the blood is decreased [19]. Mutations in FPN1 that disrupt the binding of hepcidin result in the iron overload disease type IV hemochromatosis in humans [20]. There are some data to suggest that hepcidin may be able to exert direct effects on DMT1 in enterocytes, but this has yet to be proven. The regulation of hepcidin production is complex [18], but levels are known to increase as iron stores increase and during infection and inflammation, and to decrease during hypoxia, iron deficiency and when erythropoietic needs increase. Animal models and human diseases that lead to inappropriate iron levels have helped in the elucidation of hepcidin regulatory mechanisms, although these mechanisms remain incompletely understood.