Developmental Physiology of Iron Absorption, Homeostasis, and Metabolism in the Healthy Term Infant

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Iron serves important functions in many biochemical processes including the development of the central nervous system, and it is essential to neural myelination, neurotransmitter function, neuronal energy metabolism, and neurite differentiation.[1] The requirement for iron is particularly high during periods of rapid growth and differentiation (eg, during the last trimester of pregnancy and during infancy when the brain experiences its growth spurt). Ineffective iron homeostasis during these periods may, therefore, result in delayed neurodevelopment and cognitive functions.[2] Many studies have shown an association between iron-deficiency anemia (IDA) and poor neurodevelopment in infants that lasts beyond the period of deficiency.[3] Iron supplementation reduces the risk of developing anemia in children at risk of developing iron deficiency and IDA. On the other hand, excessive iron supplementation of infants may lead to increased risk of infection, impaired growth, and disturbed absorption or metabolism of other minerals.[4] Iron is also a known pro-oxidant, and nonprotein bound iron may cause formation of free oxygen radicals. Taken together, it is important to find optimal strategies to prevent iron deficiency and avoid iron overload and its potential adverse effects. Hence, it is essential to recognize which infants should be given what form of iron, in what dose, and during which period in life to achieve optimal preventive effects with minimal, if any, adverse effects. To reach this goal, a detailed understanding of how iron homeostasis in infants and children is regulated and how regulation changes with age is a prerequisite.

Molecular Regulation of Iron Absorption

The primary importer of iron across the apical membrane of the intestinal epithelial cell is divalent metal transporter 1 (DMT1, also known as Nramp2) (**Figure**). DMT1 is essential for iron absorption because mice that lack the gene encoding DMT1 develop severe IDA.[5] This transporter is responsible for uptake of ferrous iron and is strongly regulated by iron status.[6] Although duodenal cytochrome b (Dcytb), a ferric reductase located at the apical membrane, has been shown to be involved in regulation of iron metabolism in rodents,[7] studies in knock-out mice do not support this.[8] Dcytb is not likely to be involved in iron absorption in humans because humans are known to absorb ferric iron poorly and variations in iron status (hereditary hemochromatosis, iron deficiency, controls) are not associated with changes in Dcytb expression.[9]

Once internalized by the enterocyte, iron is transported across the cell, but little is known about intracellular trafficking of iron. Depending on cellular iron status, iron may become bound to ferritin. A recent study suggests that ferritin H may be involved in protection against iron overload.[11] Over time, iron bound to ferritin will either be mobilized for further transport or lost by normal sloughing of epithelial cells.

Iron translocated across the cell is exported by ferroportin (FPN) located at the basolateral membrane (**Figure**). FPN is strongly regulated by iron status and is the only known ferrous iron exporter in mammals. FPN mutations in humans lead to iron-loading disorders.[12] Ferrous iron is oxidized by hephaestin, a copper-containing membrane-bound ferroxidase that colocalizes with FPN in the basolateral membrane.[13] This oxidation of iron is important for iron transfer because hephaestin knock-out mice develop a severe IDA.[14] Following export of iron by FPN, iron in ferric form is transported to the liver bound to transferrin and used by the reticuloendothelial system for hemoglobin (Hb) synthesis or deposited in iron stores. The communication between the iron stores in the liver and the intestinal epithelial cell was long an enigma but has been shown to be mediated by hepcidin, a peptide synthesized by the liver.[15] Hepcidin is an endocrine regulator of iron metabolism that covalently binds to FPN, which causes its internalization and breakdown.[16] Iron subsequently accumulates in the intestinal cell and downregulates the expression of DMT1. As a consequence, iron absorption is effectively downregulated.

Dcytb	Duodenal cytochrome b
DMT1	Divalent metal transporter 1
FPN	Ferroportin
Hb	Hemoglobin
IDA	Iron-deficiency anemia
MNP	Micronutrient powder

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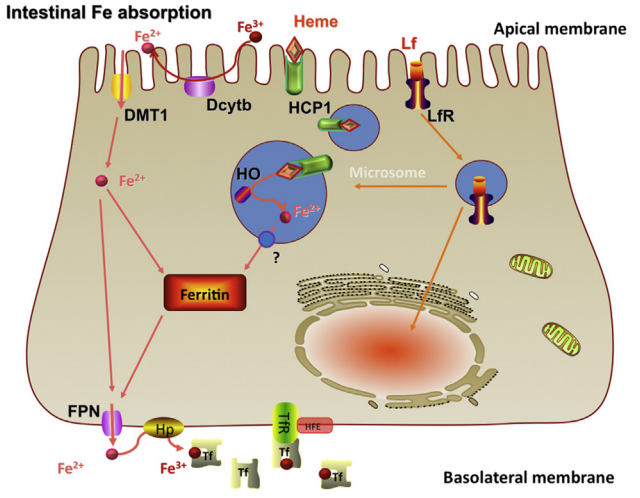

Figure. A schematic model of regulation of intestinal iron absorption including transporters at the apical and basolateral membranes as well as oxido-reduction steps involved in iron transfer. *Fe*, iron; *HCP*, heme carrier protein; *HFE*, human hemochromatosis protein; *HO*, hydroxyl; *Hp*, hephaestin; *Lf*, lactoferrin; *LfR*, lactoferrin receptor; *Tf*, transferrin; *TfR*, transferrin receptor. Reprinted with permission from Lönnerdal and Hernell, 2010.[10]

Iron Metabolism during the Newborn Period

Although the magnitude of the difference in bioavailability of iron from breast milk and infant formula varies among studies, most investigators agree that iron is absorbed better from breast milk. In part, this may be due to the presence of high concentrations of the iron-binding protein lactoferrin in breast milk and its virtual absence from infant formula.[17] A major part of iron in breast milk is associated with lactoferrin. Lactoferrin is relatively resistant against proteolysis and appears in the stool of breastfed infants in intact form.[18] Human lactoferrin is absorbed across the apical membrane of the intestinal cell by a specific lactoferrin receptor (**Figure**) and internalized with its bound iron.[19] Thus, lactoferrin facilitates a unique mechanism for absorption of iron from breast milk. In contrast, iron in infant formula based on cow milk is largely bound to casein, and phosphopeptides formed during digestion may limit iron absorption.[20] Breast milk also contains casein but in lower concentrations and with different subunits. Relatively more iron is present in low molecular complexes, a form of iron that is more likely to be absorbed. Infant formulas, particularly those for preterm infants, contain higher levels of calcium than breast milk. This has caused some concern because calcium has been shown to decrease iron absorption in adults.[21] This inhibitory effect may, however, only occur in the short term because long-term studies on infants given high levels of calcium fail to show any adverse effect on iron status.[22]

Measurements of iron absorption are dependent upon the method used. Studies using radioisotope methodology report substantial differences in iron bioavailability from breast milk and cow milk formula.[23] This method has the advantage that absorbed and retained iron is measured by whole body counting. However, iron absorption is also strongly affected by iron status, a factor that was rarely controlled for in early studies. Stable isotopes have been used more commonly in recent studies, and these studies show smaller or no differences in iron absorption from breast milk and infant formula. This may be due to improvements in infant formula composition but also may be due to methodological limitations. In stable isotope studies, it is assumed that about 80% of absorbed iron is incorporated into red blood cells,[24] an assumption based on studies of human adults. In fact, much less iron is incorporated into erythrocytes in infants,[25] which may lead to an underestimate of iron absorption. The extent to which this incorporation is affected by age or by iron status is not yet known, nor how it is affected by the form of iron given to the infant. We have shown that iron given as drops or as fortification iron affects iron indicators differently, suggesting different metabolic pathways.[26] Whether iron taken up from breast milk (lactoferrin) or from infant formula has different metabolic fates is not yet known.

Using stable isotope methodology, we showed that 6-month-old healthy, exclusively breastfed term infants absorbed 16 ± 11% of iron, with no significant difference between iron-supplemented and unsupplemented infants.[25] At 9 months of age, iron absorption from human milk remained at the same level in iron-supplemented infants (16 ± 9%). Whether there are age-related differences in iron absorption independent from iron status is not known as there have been no developmental studies on iron absorption in iron-replete infants by the same investigators using the same technique. A compilation of studies to date indicates that this is not the case as the results are highly variable, but differences in iron status and methodology between studies may obscure such a finding. Homeostatic regulation of iron absorption in infants also needs to be considered. Although no difference was found between iron-supplemented and unsupplemented infants at 6 months of age, unsupplemented infants had considerably higher iron absorption at 9 months of age (ie, 37 ± 19%).[27] This suggests that homeostatic regulation of iron absorption is absent in young infants but matures and is present at 9 months of age. In further support of this, iron supplementation between 4 and 6 months of age considerably increased Hb concentration regardless of initial iron status. In contrast, continued iron supplementation to 9 months had no effect on Hb concentrations in iron-replete infants.[28] When iron homeostasis develops during the period of 6-9 months is not yet known, nor whether it is fully developed at 9 months of age. Further studies of various age groups are needed to clarify this.

The molecular reasons for the lack of homeostasis of iron metabolism that we found in young infants are not yet known, but results from rodent models may provide some insights. It