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Intestinal iron absorption during suckling in mammals

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Abstract The maintenance of appropriate iron levels is important for mammalian health, particularly during the rapid growth period following birth. Too little iron can lead to irreversible damage to the developing central nervous system and too much iron at this point can have adverse long term consequences, possibly due to excessive free radical production. In order to maintain iron levels, intestinal iron absorption is very efficient in young mammals, such that almost all of the iron in breast milk is utilized. However this high level of absorption is unable to be down regulated in response to excess iron as it can be in adults, implying that different regulatory processes are involved during suckling. Various mechanisms have been proposed to explain this high absorption, including enhanced expression of the proteins involved in iron absorption in adults (particularly DMT1 and ferroportin), non-specific uptake via pinocytosis, and the uptake of lactoferrin bound iron by the lactoferrin receptor. However, at present the precise mechanism is unclear. It is possible that all of these components contribute to the high intestinal iron absorption seen during suckling, or a novel, as yet undescribed, mechanism could be involved. This review summarises the evidence for and against each of the mechanisms described above and highlights how little is known about iron homeostasis in this vital stage of development.

Keywords Iron absorption · Suckling · Ferroportin · Lactoferrin · Pinocytosis

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Introduction

Due to its ability to readily switch between the ferric and ferrous forms, iron is utilized by the body in many biological processes including oxygen transport, energy production and DNA synthesis. For this reason iron is an essential nutrient at any stage of life, however, it is particularly important during the rapid growth and development that occurs following birth (Domellof 2007; Collard 2009). Studies have shown that either too much or too little iron at this time can have serious and lifelong consequences. Sub-optimal levels of iron during infancy can lead to delayed cognitive and psychomotor development and at least in some cases, these neurological problems cannot be reversed by subsequent iron treatment (Lozoff and Georgieff 2006). Too much iron at this time can also have long lasting effects most likely due to excessive free radical production (Rao and Georgieff 2007; Collard 2009). A recent study has shown that increasing dietary iron in suckling rats leads to Parkinson-like neurodegeneration with age (Kaur et al. 2007). A

small human trial showed that iron supplementation of otherwise iron replete children increased the likelihood of type I diabetes developing (Ashraf et al. 2010). It is vital, therefore, that the developing infant finely regulates its iron levels to provide enough to maintain rapid growth and neurological development without risking the problems associated with iron excess. As with adult mammals, suckling animals are not known to possess a mechanism for the regulated excretion of iron and, as such, the level of iron in the body is determined at the point of absorption in the small intestine. There has been much progress in recent years in our understanding of the molecular mechanisms by which mammals maintain iron homeostasis, but much of this work has been carried out in adult mammals and the relevance of these pathways to the suckling animal has yet to be determined (Fig. 1).

Iron homeostasis during suckling

The newborn full-term human infant contains approximately 270 mg of iron (Siddappa et al. 2007) of which 10–15% is storage iron (Rao and Georgieff 2007) and, during the first few months of life,

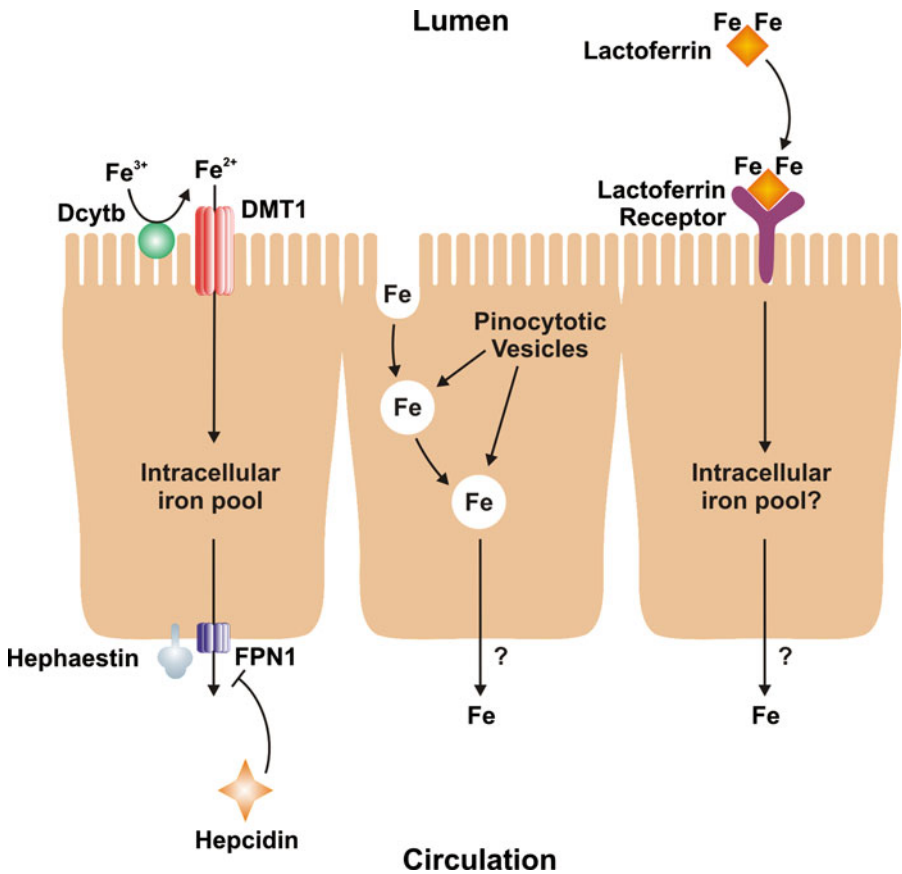

Fig. 1 Possible pathways responsible for the increased iron absorption associated with suckling in mammals. Various pathways have been proposed to be responsible for the high iron absorption seen in young mammals. The mechanism for adult iron absorption involves a ferric reductase (possibly Dcytb) and the ferrous iron importer DMT1 at the brush border, which facilitate iron transfer into the enterocyte, and the iron exporter FPN1 and the ferroxidase hephaestin to transport iron across the basolateral membrane and into the body. In adults, the basolateral transfer step is regulated by the liver-derived peptide hepcidin which downregulates FPN1 protein expression. However, absorption cannot be downregulated readily in suckling animals. Pinocytosis occurs mainly in the ileum prior to weaning and may allow the uptake of iron non-specifically from the intestinal lumen, however, how the iron then exits the enterocyte is unclear. Lactoferrin is present in breast milk and binds iron. A lactoferrin receptor has been identified on the brush border membrane of enterocytes from suckling mammals and so may facilitate iron absorption, but once again how iron exits the cell is unclear

additional iron is provided by the catabolism of fetal haemoglobin (Dewey and Chaparro 2007). In fact, full-term infants are normally endowed with approximately 45% more iron per kilogram than an average adult man (Rios et al. 1975; Rao and Georgieff 2007). Additional iron is obtained from the diet. Although breast milk does not contain high levels of iron, this iron is absorbed much more efficiently than from a mixed diet (Domellof 2007). As a result, the storage iron, supplemented by the iron obtained from breast milk, is sufficient to provide for the very high needs of the growing infant for the first 6 months (Dewey and Chaparro 2007). Following this, the introduction of complementary foods is required to provide the additional iron needed for the rapid growth that occurs at this age.

The reason for the efficient absorption of iron from breast milk is not known. Studies in humans and experimental animals have shown that suckling mammals can absorb up to 100% of a test dose and that this elevated absorption persists until weaning, after which absorption drops rapidly to adult levels of around 10% (Gallagher et al. 1973; Saarinen and Siimes 1979; Frazer et al. 2007). The decrease observed at weaning occurs despite there being no significant change in iron stores or growth rates (Anderson et al. 1991), arguing against a drop in iron demand as being the cause. In addition, evidence suggests that during the suckling period intestinal iron absorption shows little or no down-regulation in response to parenteral iron administration (Ezekiel 1967; Leong et al. 2003b). The observations that early weaning and corticosteroid treatment (Ezekiel 1967; Gallagher et al. 1973), both of which induce the premature maturation of the intestine (Herbst and Sunshine 1969), can decrease iron absorption in suckling mammals suggests that the high level of iron absorption at this time is due to a characteristic of the intestine rather than the iron in breast milk being more bioavailable, although this may be an additional factor.

Molecular mechanisms and regulation of intestinal iron absorption in adult mammals

Although the reason for the increased iron absorption in suckling mammals is unclear, the mechanism of iron absorption and its regulation has been extensively studied in adult animals. While it is not yet known how relevant these pathways are during suckling, a brief description of the molecules involved in iron absorption in mature mammals is necessary.

The intestinal absorption of iron in adult mammals is a very tightly controlled process that is regulated by stimuli that reflect the body's need for iron. Examples of such stimuli include the level of iron stores, the rate of erythrocyte production, hypoxia and inflammation (Anderson et al. 2009). An iron replete individual on a standard western diet will typically absorb around 5–10% of the iron consumed. Dietary iron is presented to the body as either haem iron or non-haem iron and the two forms are thought to enter the body via different pathways. As there is normally no haem iron present in breast milk (Collard 2009), only non-haem iron absorption will be discussed below.

Iron absorption occurs predominantly in the duodenum and proximal jejunum and is mediated by mature villus enterocytes (Frazer and Anderson 2005). Most dietary non-haem iron is in the ferric (Fe^{3+}) form and must first be reduced to ferrous (Fe^{2+}) iron in order to cross the brush border membrane. A candidate brush border ferric reductase is Dcytb (encoded by the cytochrome b reductase 1 (Cybrd1) gene) (McKie et al. 2001) but its precise role remains unclear. Ferrous iron is then transported across the brush border membrane and into the enterocyte by the iron transporter divalent metal-ion transporter 1 (DMT1) (also known as solute carrier family 11 (proton-coupled divalent metal-ion transporters), member 2, Slc11a2) (Fleming et al. 1997; Gunshin et al. 1997). The iron that enters the enterocyte has two possible fates. If the body is iron replete and the iron is not required, it is stored in the cell within cytosolic ferritin (Frazer and Anderson 2005). This iron is then lost from the body in a few days when the enterocyte is sloughed from the villus tip at the end of its life. Alternatively, if the iron is required by the body it is transferred across the basolateral membrane of the enterocyte by the membrane exporter ferroportin (FPN) (also known as solute carrier family 40, member 1, Slc40a1) (Donovan et al. 2000; McKie et al. 2000; Abboud and Haile 2000). Efficient basolateral transfer of iron also requires the ferroxidase hephaestin (Vulpe et al. 1999) although the precise relationship between FPN and hephaestin remains unclear.

The observation that iron entering the enterocyte can be either transferred to the body or remain within the cell depending on the body's needs implies that the basolateral transfer step involving FPN is the primary point at which iron absorption is regulated. Indeed, several studies have provided experimental evidence for this (Conrad and Crosby 1963; Frazer et al. 2003). One of the most significant advancements in our understanding of body iron homeostasis has been the discovery that the liver-derived peptide hepcidin plays a key role in regulating the FPN-mediated transfer of iron across the enterocytes basolateral membrane. This 25 amino acid peptide is released into the circulation by hepatocytes in response to changes in body iron demand and binds to FPN on the cell surface, thereby inducing the internalization and degradation of the transporter and decreasing iron export (Nemeth et al. 2004). Thus hepcidin is a negative regulator of iron absorption. Hepcidin also regulates the release of iron from other cell types via the same mechanism and has emerged as the master regulator of body iron homeostasis. Some excellent and detailed reviews of hepcidin action can be found elsewhere (Nemeth and Ganz 2009; Viatte and Vaulont 2009).

Iron absorption during suckling

Although the molecules described above play important roles in intestinal iron absorption in adult mammals, their role in suckling animals is unclear. We have recently shown that duodenal Dmt1 mRNA expression in rats is increased during the suckling period and decreases to adult levels around the time of weaning (Frazer et al. 2007). However, Dmt1 levels remained high in 20 day old rats even though absorption had significantly decreased at this time. Likewise Leong et al. (2003b) showed no change in duodenal Dmt1 protein expression in 10 (suckling), 20 (near weaning) and 30 (weaned) day old rats. These results suggest that duodenal DMT1 does not contribute to the high intestinal iron absorption seen in suckling animals. The result is further supported by a study using the Belgrade rat which has an inactivating mutation in the Dmt1 gene (Thompson et al. 2007). In this study Thompson et al. injected lactating dams with ^{59}Fe and examined the level of iron in the pups at 21 days. To account for any possible differences in the transfer of iron to breast milk, they fostered both Belgrade pups and wild-type littermates onto wild-type dams. They saw no change in the amount of radioactive iron in the pups and interpreted this as indicating that Dmt1 is not responsible for the high iron absorption in suckling rats. In contrast, an earlier study by Ezekiel (1967) examined the mucosal block phenomenon which describes the ability of a large oral dose of iron to reduce the amount absorbed from a subsequent dose. They showed that it was possible to induce a mucosal block in rat pups and that this persisted for at least 24 h after the blocking dose of iron. We have shown previously in adult rats that the mucosal block phenomenon is likely due to the initial iron dose triggering a rapid decrease in the expression of Dmt1 and Cybrd1 (Frazer et al. 2003). The study by Ezekiel (Ezekiel 1967) provides circumstantial evidence that Dmt1 is involved in iron absorption during the suckling period, although in this early study data on Dmt1 expression were not available. Likewise, direct absorption measurements have not been carried out in Belgrade rat pups so the role of DMT1 in iron absorption at this time remains unclear.

The role of Fpn is equally unclear. Our laboratory and others have shown that Fpn message and protein do not change in the duodenum over the weaning period, suggesting that differences in Fpn expression are not responsible for the differences in iron absorption (Leong et al. 2003a, b; Frazer et al. 2007). However, when we examined Fpn expression in the distal alimentary canal we found that Fpn is expressed throughout the small intestine and into the colon in suckling rats and that this expression pattern became restricted to the proximal small intestine following weaning (Frazer et al. 2007). This correlated well with iron absorption from isolated intestinal segments where absorption was increased in the distal small intestine and colon of suckling rats relative to post-weaning animals. Further support for a role for Fpn in iron absorption during suckling was reported by Donovan et al. (2005) using an inducible intestine-specific Fpn knockout mouse. Detailed analysis of the suckling knockout has not been carried out, however, the study showed that pups with reduced Fpn expression were visibly paler late in the suckling period. This implies that intestinal Fpn is required to prevent iron deficiency anaemia occurring in suckling animals, presumably because it is required to absorb iron

from breast milk. Unfortunately these mice were not examined any further to confirm this nor was intestinal iron absorption measured directly.

Expression of the iron regulatory peptide hepcidin is very low during the suckling period but increases rapidly to adult levels following weaning (Frazer et al. 2007). As hepcidin is a negative regulator of Fpn expression, this would fit with Fpn playing a role in iron absorption during suckling. However, despite the increase in hepcidin expression on weaning, when iron absorption declines dramatically, there is no change in Fpn mRNA or protein levels in the duodenum (Leong et al. 2003a, b; Frazer et al. 2007). Other changes in Fpn function, such as those related to its localization or activity cannot be ruled out. Furthermore, it has been shown that suckling mammals cannot down-regulate their iron absorption in response to iron loading (Ezekiel 1967; Leong et al. 2003b), raising the question of why, if the Fpn/hepcidin axis is functional at this time, is Fpn not down-regulated in response to increasing iron levels as would normally occur in adults. Clearly more research is needed before it can be concluded that the adult absorptive machinery is or is not responsible for the extremely high iron absorption seen in the suckling mammal.

Although the adult iron absorption pathway is the most obvious mechanism by which suckling mammals could absorb iron, other possible explanations have also been suggested. One involves the high capacity of the distal part of the immature intestine to take up large molecules, such as antibodies, by pinocytosis (Clark 1959). The pinocytotic capacity of the intestine declines with intestinal maturation, leading to the suggestion that the non-specific uptake of iron by pinocytosis may explain the increased iron absorption in the suckling animal (Ezekiel 1967). Pinocytosis also decreases in response to corticosteroid treatment, and this may explain the decrease in absorption that accompanies such treatment (Clark 1959). Several observations, however, suggest that this is not the case. Firstly, pinocytosis occurs predominantly in the ileum of the suckling rat (Clark 1959) whereas the duodenum is quantitatively the most important site of iron absorption, as it is in the adult. Secondly, the absorption of increasing doses of oral iron indicates that the mechanism of uptake is saturable in suckling animals (Gallagher et al. 1973). Thirdly, the ability of the immature proximal intestine to exclude ^{51}Cr–EDTA, a non-absorbable marker, supports the idea that, at least in this portion of the gut, non-specific uptake is not occurring (Srai et al. 1988). Other studies have shown that although pinocytosis increases the uptake of iron into the ileum, the amount transferred to the body is similar to that of an adult, indicating that the iron taken up by immature enterocytes is not available for use by the body (Gallagher et al. 1973). Therefore, pinocytosis may play some role in the high iron absorption seen during the suckling period, but it is unlikely to account for the majority of the iron absorbed.

The milk protein lactoferrin has also been suggested to play a role in iron absorption prior to weaning. Lactoferrin is a member of the transferrin family of proteins and is a major iron binding protein in breast milk (Kawakami and Lonnerdal 1991). It is known to have a bacteriostatic effect and it has been suggested that this is its primary role in milk (Ellison and Giehl 1991; Qiu et al. 1998). However, it is also resistant to proteolysis making it an ideal carrier for iron in the lumen of the gastroenterological tract (Davidson and Lonnerdal 1987). In addition, the lactoferrin receptor is expressed on the brush border of intestinal enterocytes and is higher in expression in these cells in suckling animals and humans (Kawakami and Lonnerdal 1991; Suzuki and Lonnerdal 2002). Despite this promising role for lactoferrin, the high absorption of orally administered radioiron in suckling rats does not require the presence of lactoferrin, although it is possible that residual lactoferrin present in the gut may be enough to facilitate absorption (Frazer et al. 2007). The major evidence against lactoferrin playing a role in iron absorption during suckling comes from the lactoferrin knockout mouse. Lactoferrin knockout pups born to lactoferrin knockout mothers did not have reduced iron stores when examined late in the suckling period (Ward et al. 2003). Indeed liver iron stores and transferrin saturation were higher in the knockout animals. However, total body iron levels were not directly measured in this study so it is possible that lower total body iron levels were masked by a redistribution of iron due to the absence of lactoferrin in the pups. In addition, intestinal absorption was not directly measured so a role for lactoferrin in iron absorption in suckling animals cannot be completely ruled out.

Another factor that may contribute to the high level of iron absorption in the suckling infant is the

gut microbiota. It is known that the bacterial flora of breast fed infants consists predominantly of *Bifidobacterium* species (Fanaro et al. 2003), whereas members of the *Firmicutes* and *Bacteroidetes* predominate in adults (Eckburg et al. 2005). Many *Bifidobacterium* species are not inhibited by the bacteriostatic properties of lactoferrin, and the growth of some is actually enhanced in the presence of lactoferrin (Kim et al. 2004). A recent study has shown that the addition of *Bifidobacterium* species to milk as a probiotic decreases the incidence of iron deficiency in young children (Sazawal et al. 2010). Although the mechanism for this effect is unknown, it was suggested that the use of probiotics could reduce enteric infections resulting in better iron absorption. Whether, and to what extent, the microbial flora of the suckling intestine contributes to the high level of iron absorption seen at this time has yet to be determined.

Conclusions

There is substantial evidence demonstrating the importance of an appropriate supply of iron during the developmental period in mammals, and clinical consequences may accompany both too little iron and too much iron. Suckling animals are particularly susceptible to iron related pathologies, predominantly due to inadequate dietary iron. However, they can also accumulate excess iron rapidly if it is supplied to the gastrointestinal tract due to their extremely efficient iron absorption and their inability to down regulate this process. The mechanism responsible for the efficient absorption of iron from breast milk by suckling mammals remains to be determined. While it is possible that other, as yet uncharacterized, transport systems may play a role in the increased iron absorption during the suckling period, it is likely to involve one, or perhaps most likely, several of the potential mechanisms described above. Redundancy in the system could explain why these mechanisms, individually at least, appear dispensable. Clearly more research is required to fully understand how iron transverses the epithelium of the gastrointestinal tract during this important stage of development.

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