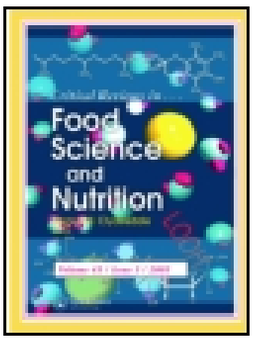

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Iron influences on the Gut-Brain axis and development of type 2 diabetes

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Abstract

BACKGROUND: Microbiota/neuroendocrine interactions with health and disease are increasingly recognized.

MAIN BODY: Aging is associated with progressive iron storage and development of type 2 diabetes, which impacts on brain microstructure and function, mainly in obese subjects. Iron status is also mutually influencing the composition of the gut microbiota, which in turn may affect cognition through the gut-brain axis.

SHORT CONCLUSION: In this article we update the possible role of iron in all these interactions.

Keywords

Iron, brain, microbiota, gut, obesity.

BACKGROUND

Iron is the most abundant metal in the human body. No independent life forms on earth can survive without iron. Iron mainly works as a cofactor for proteins such as hemoglobin and various enzymes, being intimately involved in binding and transport of oxygen. Importantly, iron has proven to be fundamental in the selection imposed by evolution, given this close relationship with oxygen. Iron also intervenes in the regulation of DNA synthesis, cell growth and differentiation, electron transport and many important metabolic processes [1].

Recent systematic reviews disclosed that type 2 diabetes (T2D) and cardiovascular disease are significantly influenced by both iron excess and iron deficiency [2-4]. Iron is known to affect whole body economy through its interactions with glucose metabolism in the main insulin sensitive tissues (muscle, liver and adipose tissue) as extensively reviewed elsewhere [2,3]. The pathophysiology of abnormal glucose metabolism can be also connected to other emerging scenarios.

Bidirectional communications between the brain and the gut has long been recognized. The brain controls directly hepatic gluconeogenesis and glucose uptake in response to input from insulin as well as other hormones and nutrients [5,6]. The gastrointestinal tract continuously communicates with the brain, especially with the hypothalamus. It is now well established that the cross talk between the gut and the brain is of crucial importance in the control of glucose homeostasis [7]. Iron could induce disturbances in the gut-brain axis glucose sensing process contributing to the pathogenesis of T2D. Iron could also contribute to the impaired cognitive dysfunction that is associated with the disease. Brain iron overload can contribute to

insulin resistance (i.e. the disruption of the insulin signaling in neuronal cells) and oxidative damage favoring the cognitive impairment [8-10]. Iron accumulation in the brain has long been suspected to be involved in the pathogenesis of cognitive dysfunction but only recently has been shown to play a role in obese patients [11].

The human intestine harbors nearly 100 trillion bacteria that are essential for health. Recent studies reveal the importance of gut microbiota to the function of the central nervous system [12]. A hot topic is also the potential influence of gut microbiota on systemic metabolism. The interest in the mammalian gut microbiota and its implications for the host health has increased tremendously during the past decade with the recognition of the role of microbiota in the pathogenesis of obesity, cardiovascular and metabolic diseases [13]. This transition metal has a fundamental role in the host-microbiota dialogue and, by virtue of this role, potentially on host energy metabolism. Iron availability modulates the gut microbial communities [14,15] which, in turn, might promote obesity and insulin resistance. Gut microbiota, conversely, influence dietary iron absorption [16-19] and innate immunity function [20,21]. All these scenarios (Figure 1) are reviewed below.

MAIN TEXT

Iron and the brain

Extracellular iron in the central nervous system is bound to transferrin and internalized into the cell via a transferrin receptor based endocytosis and the channel divalent metal transporter 1 (**cDMT1**). Cytosolic iron is stored in ferritin complexes and hemosiderin which serves as a buffer against harmful iron deficiency or overload. It is also transferred to organelles that are rich

in iron such as mitochondria that have their own iron importers and store iron in mitochondrial ferritin. No mitochondrial exporters have been discovered so far, suggesting that the major mechanism for iron recycling is via mitophagy and lysosomal degradation of iron-containing proteins. The possible role of mitochondrial ferritin in the context of brain iron overload is unknown. Cellular iron is exported via ferroportin with the support of ferroxidases, ceruloplasmin, mostly in the astrocytes and hephaestin, which is widespread. Transcription of **cDMT1** and ferritin are closely controlled via iron regulatory proteins (IRP) [8,9]. The brain exhibits a high iron demand. The metal is an essential trace element vital for normal brain metabolism and plays an important role in oxygen transport, myelin production, neurotransmitter synthesis, and the Fenton reaction that is, in turn, crucial to oxidative stress [2,3]. The *substantia nigra* and the *globus pallidus* naturally contain the highest concentrations of iron [8-10]. Ferritin bound iron, in the course of normal aging, accumulates in the brain until the 4th decade of life [22]. High iron concentration in the basal ganglia constitutes a marker for tissue damage in several neurologic disorders [8,9]. High iron requirements coupled with the extraordinary brain susceptibility to iron-generated damage through reactive oxygen species. A stringent regulation of the availability of iron in the central nervous system is thus implied. Brain iron accumulation and consequent oxidative damage has been increasingly recognized to be involved in early cognitive dysfunction [8-10]. Interestingly, obesity, and especially android fat mass, are associated with cognitive decline [11, 23-25]. Information about the possible influence of insulin resistance on brain iron deposition however is scarce.

Diet-induced obesity increases the levels of reactive oxygen species in the brain of mice worsening their cognitive performance [26]. Rats fed a high-fat diet show progressive insulin

resistance which **runs** in parallel to iron deposition in the *substantia nigra* [27]. Similar events in humans have been unexplored. Upregulation of known obesity related genes (the insulin receptor and the glucagon-like peptide-2 receptor genes) and altered expression of genes involved in various metabolic processes **have** been demonstrated in the caudate nucleus of rhesus monkeys with increased fatness [27-29].

All these observations constitute an important issue because T2D is well known to be associated with a 1.5-2.5-fold increased risk of dementia [23-25]. Iron overload could favor cognitive deficits that typically develop in T2D. A syndrome of insulin resistance clustered with metabolic abnormalities and increased hepatic iron concentration (HIC) is well known [2-3]. Iron is expected to accumulate in parallel to its reserves in the different tissues. A magnetic resonance imaging (MRI) study showed a parallel increase in liver and brain iron concentration in the elderly, suggesting that iron levels in specific gray matter brain regions are influenced by systemic iron dysregulation [11]. In middle-aged obese subjects without diabetes there was also a significant increase of iron signal in the caudate and lenticular nucleus, hypothalamus and hippocampus. HIC and brain-iron overload estimated by MRI correlated positively, mainly at the caudate, hypothalamus, and hippocampus of these subjects. The area under the curve of insulin during the oral glucose tolerance test was independently associated with iron signal at the caudate and hippocampus. At the functional level, HIC and iron signal at the caudate, hypothalamus, and lenticular nucleus were independently associated with worse cognitive performance [11]. In this sense, the hippocampus and caudate nucleus are known to be involved in the planning and execution of strategies, behaviors that are required for achieving complex goals, and memory functions [11]. The hypothalamus plays a role in emotional regulation and

vital functions [10]. All these regions are connected with the prefrontal cortex and frontal cortical areas, brain regions that usually are associated with cognitive and executive functions [10]. The structural damage due to iron overload in these nuclei might produce a disruption of cortical projections that could impact the cognitive performance. A relatively hypometabolic state of the blood-brain barrier in obesity and aging could be a predisposing factor for the iron deposition [30], that in turn would trigger oxidative stress and lead to neuronal death (Figure 1).

Iron and the gut

The small intestine, principally the duodenum, is of fundamental importance for the homeostasis of iron through the regulation of its absorption. Dietary iron enters the body primarily through duodenal enterocytes, polarized cells which express both the **cDMT1** and the cytochrome b ferrireductase(Dcytb) on their apical membrane. Heme uptake, while constituting a significant iron source for many mammals, requires heme carrier protein 1 (SLC46A1). Export of the metal from these cells occurs via the basolateral transporter FPN which transports ferrous iron. The export pathway before described is driven by the oxidation of iron at the basolateral, exosolic leaflet by hephastin, with considerable homology to Ceruloplasmin [2].

Old studies showed that alterations in the gastrointestinal tract and villous atrophy were associated with iron deficiency [31]. Iron deficiency, in turn, may also lead to alterations in intestinal permeability [31], decreasing the absorption of D-xylose [32] and altered activity of intestinal disaccharidases [33]. In murine models, iron deficiency affects gut glucose homeostasis through alterations of intestinal permeability and activity of disaccharidases. In rats, there is also a decreased activity of intestinal disaccharidases with iron deficiency [33,34]. Iron

deficiency was found to decrease the absorption of glucose, sodium, and water while increasing SGLT1 mRNA in the intermediate and distal segments of the small intestine of rats [35] in *in vitro* models that evaluated the intestinal trans epithelial transport of glucose using the intestinal perfusion method (a model which enables the maintenance of physiologic conditions such as vascularization, intestinal motility, and hormonal interactions). These results were difficult to justify but parallel to what has been observed in the eukaryotic yeast Saccharomyces cerevisiae [35]. In the latter, the iron-deficiency-induced Cth2 protein accelerates the degradation of mRNA-encoding proteins which participate in various metabolic processes depending on iron in a post-translational mechanism of downregulation [36]. Cth2 and Cth1 proteins are also related to upregulation of the mRNAs involved with glucose capture, glycolysis and metabolism of carbohydrates [36].

The higher relative SGLT1 mRNA levels in anemic rats, associated with a decrease in the intestinal trans epithelial transport of glucose, suggested to the authors the existence of a post-translational regulator that is altered in the presence of iron deficiency, as demonstrated with the proteins Cth2 and Cth1. The alteration in intestinal transport of glucose and sodium may also be explained by the impaired functioning of the sodium–potassium pump located in the basolateral membrane of the enterocyte, bearing in mind the decrease in sodium–potassium–adenosine triphosphatase activity observed in the presence of iron deficiency [37]. On the other hand, another study on differential analysis of the rat intestinal proteome evidenced that, following dietary iron deficiency, significant changes in the levels of proteins belonging to glucose and fatty acid metabolism were significantly altered [38].

Despite all these evidences in animal models, the impact of iron deficiency on iron absorption in humans has not been studied in detail and merits further research.

Regulation of iron absorption by the gut

Physiologically, the most important modulator of intestinal iron absorption is hepcidin [39]. Hepcidin is a 25-amino acid peptide hormone secreted from liver in response to iron overload and inflammation that reduces ferroportin levels, blunting iron export from enterocytes into bloodstream and inhibiting intestinal iron absorption [39-41]. Even though in humans, the negative effects of serum hepcidin on intestinal iron absorption are well demonstrated [42-44], the possible mechanism has been less investigated. Only a recent study that uses ex vivo human intestinal organ culture demonstrated that hepcidin administration reduced *FPN1* and *DMT1* mRNA and protein levels in human intestine [45]. Interestingly, serum hepcidin was significantly reduced in patients with type 2 diabetes, after controlling for obesity [46-49]. The inductor effects of insulin on hepcidin biosynthesis [50] might explain these observations. In rats, the reduction of serum insulin levels by streptozotocin administration resulted in increased serum and tissue markers of body iron accumulation in parallel with increased intestinal ferroportin levels and iron absorption and decreased serum hepcidin levels [50]. Of note, these parameters were normalized with insulin therapy, and *in vitro* experiments confirmed insulin-induced hepcidin biosynthesis [50]. However, additional studies are required to investigate the relathionship between intestinal markers of iron absorption and serum hepcidin in patients with type 2 diabetes.

Iron and gut microbiota

Microbes belonging to phyla Firmicutes and Bacteroitedes and, to a lesser extent, Actinobacteria constitute the main phyla in human gut. The Firmicutes include genera belongings to the Clostridium clusters IV and XIV such as Eubacterium, Faecalibacterium, Roseburia and Ruminococcus and Lactobacillus. The Bacteroitedes include the genera Bacteroides and Prevotella. The mechanisms whereby the relative abundance of these gut microbiota communities at the phylum and genus level contributes to the disruption of glucose metabolism remain to be clearly elucidated. Bacterial fermentation however, results in the production of short chain fatty acids (SCFAs, Acetate, Butyrate, and Propionate) that are able to modulate insulin sensitivity and secretion through various metabolic pathways. For instance, Propionibacteria enhanced colonic iron absorption through the biosynthesis of propionate (51). SCFAs, importantly, influence gut permeability whereas reduced permeability leads to endotoxemia, low-grade inflammation and activation of the innate immune system cascade. SCFAs bind to and activate G-protein-coupled receptors (namely Gpr41, Gpr43 and Gpr120) on colonic and enteroendocrine cells regulating local release of glucagone like peptide and Peptide YY [52]. Receptors located on beta cells and sympathetic ganglia inhibits insulin release and enhances sympathetic activity by binding to Gpr41 [53].

Microbes also produce some bile acids that are able to impact significantly on the insulin signaling [54]. It has been shown, finally, that microbial colonization influences suppression of molecule expression such as FIAF (fasting induced adipocyte factor) that regulates lipoprotein lipase activity in adipocytes and adenosine monophosphate activated protein Kinase (AMPK) which, in turn, up-regulates fatty acids oxidation in skeletal muscle and glycogen storage in the liver [13].

Iron status, in this context, can modulate glucose homeostasis by virtue of its link to gut microbiota. The latter modulates absorption of several micronutrients including iron [16] while iron availability affects gut microbiota composition and metabolic activities [55] as well as gut immune system functionality [21]. The best characterized micronutrient in terms of its interaction with both the microbiota and the immune system is iron [21]. Germ-free but not conventionally raised rats become anemic when fed a low-iron diet. The germ-free rats also show increased loss of iron in their feces compared with their conventionally raised counterparts [16]. One study found that in the absence of a viable intestinal microflora the absorption and net retention of iron decreased about 25% [16]. These studies are in agreement with others that found decreased absorption of iron after antibiotic treatment in rats [19] and rabbits [56]. Other investigators, however, described that germ-free mice absorbed more of a test dose of ^{59}Fe over a 7 day period [18]. Iron deficiency also impairs innate immune responses, as it is required for the respiratory burst [20]. Iron-deficiency anemia, interestingly, has been also associated with increased susceptibility to bacterial endotoxin [20]. Depending on dietary availability, only ~5-15% of iron is absorbed and the remainder passes into the colon, where it is available for the gut microbiota. The micronutrient iron is essential for most gut bacteria [57] except lactobacilli, which are able to grow without iron in a nucleotide-rich medium [57]. Bacteroides, on the other extreme of the spectrum, are strongly dependent on heme [57] and in iron depletion, heme availability in the gut is likely to be limited. Iron availability, thus, deeply influences gut bacterial ecosystem.

Mechanistic studies

Different studies have investigated the effect of iron deficiency and iron supplementation on the gut microbiota. Infants given an iron-fortified cow's milk preparation had lower isolation frequencies of bifidobacteria but higher counts of Bacteroides spp. and Escherichia coli than children receiving an unfortified cow's milk preparation in 2 investigations which used culture methods [58,59]. Other authors, using molecular methods, found lower amounts of lactobacilli and higher concentrations of Enterobacteriaceae in fecal samples of children from Côte d'Ivoire receiving iron-supplemented biscuits compared with a control group receiving nonsupplemented biscuits [60]. Iron deficiency in young women in India, in contrast, was associated with low levels of lactobacilli belonging to the Lactobacillus acidophilus group [61]. A systematic review, in fact, found that iron supplementation in children was associated with a slight but significant increased risk for diarrhea [62]. Experimental studies in animals have shown that total anaerobes, Enterococcus spp. as well as Lactobacilli were elevated in iron-deprived mice and iron supplementation generally perturbed the gut microbiota [63]. Iron deficiency in young Sprague-Dawley rats, increased Enterobacteriaceae and Lactobacillus/Leuconostoc/ Pediococcus spp., but decreased Bacteroides spp. and Roseburia spp./Eubacteriumrectale members. The gut microbiota metabolites propionate and butyrate were significantly decreased during iron deficiency along with the bacterial composition changes, with a loss in microbial diversity with iron depletion. Iron supplementation with FeSO4 and electrolytic iron partially re-established the original gut microbiota composition and led to a full recovery of metabolic activity in the rats [64].

Mechanisms by which gut iron availability influences potentially whole body glucose homeostasis encompass the interplay between microbiota and secretion of bile acids. Bile acids are important in regulating glucose metabolism and the biliary system may have as yet

underappreciated effects to modulate glucose homeostasis [65]. Bile is introduced into the duodenum, a site of active iron absorption and creation of an iron-scarce environment. Bacteria must resist the antimicrobial properties of bile in order to survive in the small intestine. Bile salts act aids in digestion through emulsification of fatty foods and these detergent properties allow bile to disrupt the membranes of bacteria. Bacteria that have adapted to life in the intestine have developed mechanisms of resistance to bile, including efflux pumps that are able to transport bile out of the cell [66].

In a recent study it was demonstrated that bile salts caused increased mRNA levels for seventeen genes associated with iron scavenging and metabolism, and counteracted the inhibitory effect of the iron chelating agents in *E. coli* [67]. *E. coli* O157:H7 might use bile as an environmental signal to adapt to changing conditions associated with the small intestine, including adaptation to an iron-scarce environment. Thus, the study of the interactions among bile acids, gut microflora metagenome and glucose metabolism may uncover unsuspected relationships. In a bidirectional switch, genetic modification of host proteins involved in iron metabolism seems to affect the composition of intestinal bacteria. The microbiota of Irp2-/- mice was enriched in Lactobacillus murinus and Lactobacillus intestinalis, while Enterococcus faecium species cluster was highly abundant in Hfe-/-mice [68]. However, this investigation evaluated only a selected spectrum of the fecal microbiota.

CONCLUSIONS:

Emerging evidence suggests that the link between iron and glucose metabolism is not confined just to classical insulin sensitive tissues but also involve the brain-gut axis (Figure 2). The

maintenance of an adequate iron status might be beneficial to the preservation of the glucose homeostasis and, in the long-term, to reduce the burden of cognitive dysfunction associated with T2D. It would be tempting to investigate whether the dietary iron supplementation modulates glucose homeostasis by inducing changes of the gut microbiota. An in depth study of iron homeostasis in the general population, and in T2D patients, may help to design an optimal gut microbiota composition, disclose unsuspected relationships with bone frailty and may even impact on early cognitive dysfunction. The focus of the research should move toward investigation of the optimal iron status, preferably using a multidisciplinary approach. Investigation seems particularly important in subjects at risk of developing T2D and must be not limited to classical insulin sensitive tissues. In this regard, the utility of MRI as a surrogate marker of iron metabolism should be explored further [11]. **Furthermore, whether the exclusion of duodenum and part or totality of the jejunum as after gastric bypass or bilio-pancreatic diversion might account, at least in part, for the changes (and possibly association) in gut microbiota, iron anemia and insulin resistance improvement. This should be investigated in depth in future studies.**

DECLARATIONS

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

J.M. F-R., J.M. M-N. & M.M wrote the manuscript. All authors read and approved the final manuscript.

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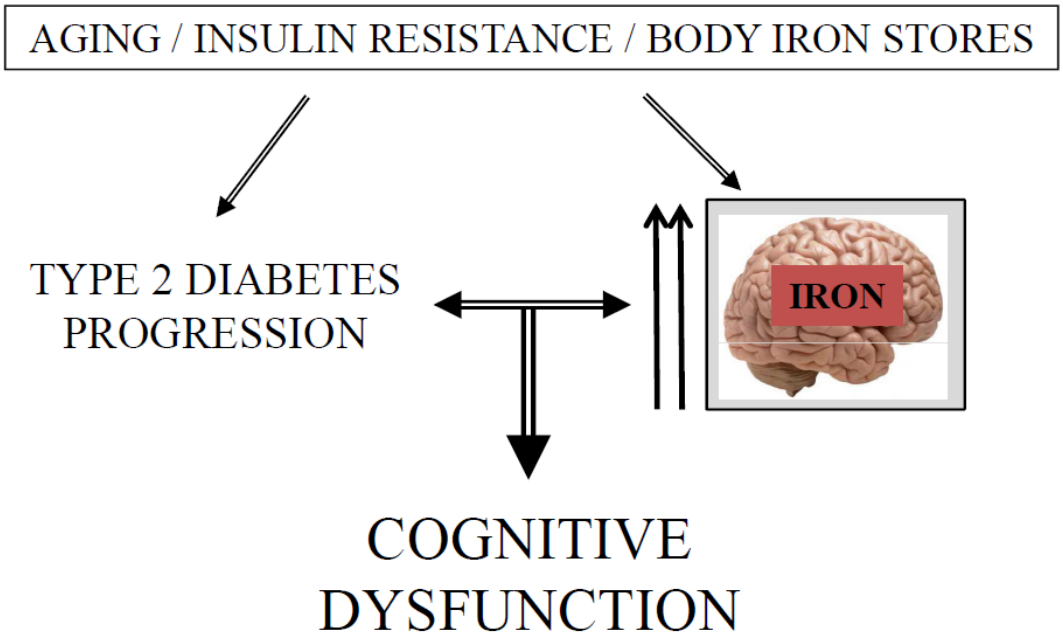

Figure 1. Insulin resistance, linked to increased body iron stores, might result in increased brain iron accumulation in parallel to type 2 diabetes progression. The consequence would be the induction of alterations in brain structure and cognitive dysfunction.

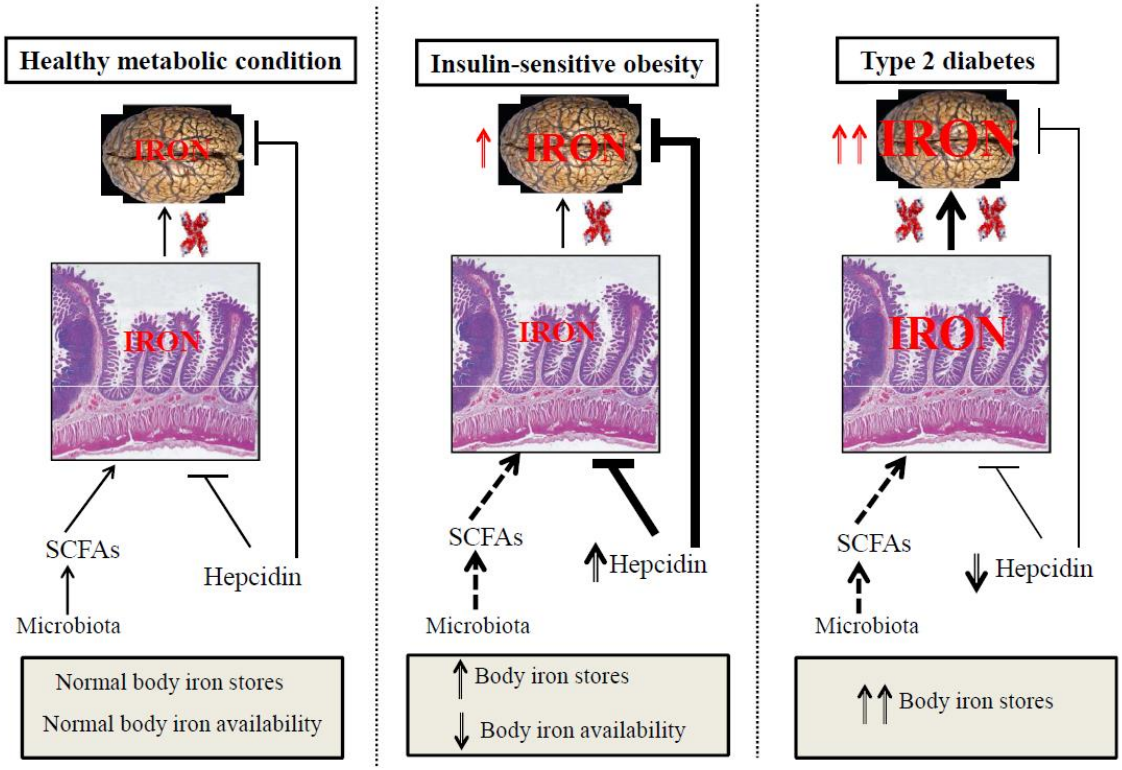

Figure 2. Main factors that modulate intestinal iron absorption (short chain fatty acids (SCFAs) and hepcidin) and their contribution to several metabolic conditions (obesity and type 2 diabetes) in parallel to body iron stores.