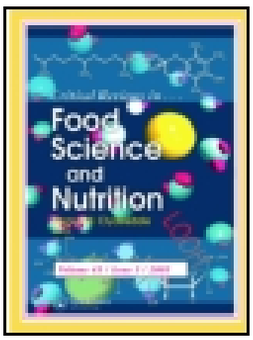

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REVIEW

Interaction between iron and omega-3 fatty acids metabolisms: where is the cross-link?

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ABSTRACT

Iron is an essential micronutrient for almost all living organisms. It plays an important role in DNA, RNA, and protein synthesis and takes part in electron transport, cellular respiration, cell proliferation and differentiation, and gene expression regulation. However, there is a fine line between excessive and insufficient body iron content. Iron overload is biochemically dangerous. It causes serious toxicities and generates reactive oxygen species via the Fenton reaction, leading to damage to cellular membranes, proteins, and DNA. Omega-3 fatty acids play an essential role in many physiological processes, including energy metabolism and signal transduction, as well as acting as structural components of cell membranes. Omega-3 fatty acids also help to maintain homeostasis and combat diseases. Recent studies using model organisms as well as clinical studies have revealed a link between omega-3 fatty acids and iron metabolism. Moreover, various iron-related disorders are significantly affected by omega-3 fatty acids. There is a clear relationship between iron and omega-3 fatty acid metabolisms; however, the underlying mechanisms are unknown. Therefore, in-depth research is needed to determine the exact nature of the metabolic interactions of these nutrients. Here, we focus on iron and omega-3 fatty acid metabolisms at their crossroads in the liver and brain.

KEYWORDS

Iron metabolism; omega-3 fatty acid metabolism; ferroptosis; oxidative stress; inflammation; nonalcoholic fatty liver disease

Introduction

Maintaining iron homeostasis is critical for all cells in the body, as both iron insufficiency and overload may pose a potential risk of cellular death. Iron is indispensable in humans due to its unique redox properties, which determine the functions of many enzymatic and non-enzymatic proteins involved in biochemical processes, such as oxygen transport, DNA and collagen synthesis, and cell proliferation and differentiation (Crichton and Ward 1992). Yet, those same redox properties of iron are used to generate highly reactive oxygen-free radicals. Therefore, both intracellular and systemic iron homeostasis must be tightly controlled and balanced to ensure that the body meets its iron needs, while also preventing toxicity. Because of iron's biological duality, it is often referred to as a "double-edged sword." Likewise, omega-3 fatty acids play essential roles in number of physiological functions, including energy metabolism and signal transduction, and they act as key structural components of cell membranes. Importantly, results from recent in vitro and in vivo animal studies, as well as data from clinical cases and trials, clearly demonstrate a link between iron and omega-3 fatty acid metabolisms.

Iron metabolism

Iron, after aluminum, is the second most abundant metal on Earth, representing about 5% of the earth's crust (Pantopoulos et al. 2012). It is an essential element for almost all living organisms, except for some strains of Lactobacillus (Weinberg 1997). The two most common iron oxidation states are the divalent ferrous (Fe^{2+}) and the trivalent ferric (Fe^{3+}). Iron's ability to easily undergo redox cycling between its oxidation states underlies its importance as a cofactor of a number of enzymatic and non-enzymatic proteins (Wallace 2016). Within the human body, iron is required as a cofactor for many hemoproteins and non-heme iron-containing proteins. The main hemoproteins include myoglobin and hemoglobin, which are responsible for oxygen binding and transport. Antioxidant enzymes (e.g., catalase, peroxidases) and enzymes involved in electron transport and mitochondrial respiration (i.e., cytochromes) are also proteins that contain heme in their active centers. One percent (1%) of body iron is incorporated into proteins containing iron–sulfur clusters, which have crucial functions in DNA synthesis, cell proliferation and differentiation, gene regulation, drug metabolism, and steroid synthesis (Crichton and Ward 1992). The intracellular pool of free iron, which is a reservoir for heme synthesis and is incorporated into iron-containing proteins, also exists in the so-called labile iron pool (LIP). This pool of iron includes the cytoplasmic chelatable, redox-active, and transitory iron pool, which serves as a crossroads for cell iron metabolism. LIP is also considered a pool of iron with the capacity to promote the formation of reactive oxygen species (ROS) *via* the Fenton reaction of hydrogen peroxide (H_2O_2) and Fe^{2+} (Meneghini

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1997; Winterbourn 1995). The most toxic form of ROS produced through Fenton chemistry is the hydroxyl radical ($^{\bullet}OH$), which has no known specific cellular scavenger, and in turn can cause severe damage to the main cellular biomolecules, such as protein modification, DNA breakage, and lipid peroxidation (Meneghini 1997).

$$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + HO^- + {}^{\cdot}OH$$

Defense against the toxic effects of Fe and O_2 derivatives is mainly provided by two specialized Fe-binding proteins: extracellular transferrin (Tf) and intracellular ferritin (Ft). Both proteins retain iron in the form of Fe^{3+} ions, making them safe and non-available for the Fenton reaction, and in consequence for the production of free radicals. However, in several iron overload syndromes, such as hereditary hemochromatosis (HH) or thalassemia, when the capacity of Tf to bind iron is overwhelmed, non-transferrin bound iron (NTBI) appears in the blood plasma. The exact chemical nature of NTBI remains elusive, but its redox reactivity and toxicity are well established. It may consist of Fe^{3+} loosely bound by albumin or by small organic molecules, such as citrate (Harris 2002). Recent evidence has shown that NTBI enters parenchymal cells *via* the NTBI transporter ZIP14, increasing LIP, and as mentioned above, exacerbating oxidative stress and therefore increasing toxicity (see Knutson 2019 for comprehensive review).

The average total amount of iron in the body of an adult man varies from 3.5 to 5 g (Yiannikourides and Latunde-Dada 2019). Most body iron is embodied in hemoglobin (60%), myoglobin (5%), and iron-related enzymes (5%), and much of it is safely stored in Ft (20%) and hemosiderin (10%), mainly in hepatocytes (Benito, House, and Miller 1998). Every day, 1–2 mg of iron from the diet is transported by absorptive enterocytes in the duodenum. Erythropoiesis, by means of intensive hemoglobin synthesis occurring in the erythrocyte precursors, is the process with the highest demand for iron (20 mg daily).

Iron absorption

The amount of daily absorbed iron is dynamic and depends on health, sex, and age. It is thought that on average, only 10% of 15 mg of iron contained in the European diet is absorbed (Waldvogel-Abramowski et al. 2014). The human body's rate of iron absorption appears to respond to factors, such as iron stores and intensity of erythropoiesis in the bone marrow. Iron absorption is reduced under inflammatory conditions in order to impair the proliferation of tumor cells or invading microbes; thus, it strengthens cell-mediated immunity against the invading pathogens. Sequestering iron from bacterial invaders that colonize the vertebrate host is a central feature of nutritional immunity and the "fight over transition metals" at the host-pathogen interface. The iron-containing proteins of gram-negative bacteria, such as *Escherichia coli*, are estimated to comprise 85% of the metalloproteome, which itself accounts for ~30 % of the entire proteome (Waldron et al. 2009). However, iron absorption from the diet increases in the last trimester of pregnancy, when the fetus itself and the placenta require about 360 mg of iron per day, which must be absorbed by the mother and transported through the placenta for fetal growth and development (Bothwell 2000).

There are two types of dietary iron: heme iron and non-heme iron. Heme iron is derived from the hemoglobin and myoglobin of animal sources and is absorbed with greater efficiency than non-heme iron derived from plants and iron-fortified foods, largely existing in the ferric form.

Heme-containing proteins are released from food under the condition of the low gastric pH. Then, heme is extracted from hemoglobin and myoglobin by proteolytic activity in the stomach and duodenum (Yiannikourides and Latunde-Dada 2019). Intestinal heme uptake occurs in the proximal part of the duodenum. The first step in heme iron absorption involves the transport of intact heme across the apical membrane of the enterocyte *via* the heme carrier protein 1 (HCP1) (Shayeghi et al. 2005). However, it is now well established that this protein is the proton-coupled folate transporter (PCFT/*SLC46A1*). Nevertheless, some authors do not exclude a dual function for PCFT in both folate and heme transport (Le Blanc, Garrick, and Arredondo 2012; Qiu et al. 2006; Schaer et al. 2008). Another candidate for heme import is heme-responsive gene 1 (HRG1, *SLC48A1*), previously identified as a heme importer in the intestine of *Caenorhabditis elegans* (Rajagopal et al. 2008). After being transported into the enterocyte, heme follows two separate pathways. First, intracytoplasmic heme can be catabolized by heme oxygenase 1 (HO1), in the process leading to the release of ferrous iron, which transiently enriches LIP and may be then neutralized by Ft, a cytosolic multimeric iron-storage protein, or recycled to the circulation across the basolateral membrane of the enterocyte. The second, minor pathway of heme iron movement involves the export of the intact heme molecule across the basolateral membrane by feline leukemia virus subgroup C cellular receptor 1 (FLVCR1) to the blood plasma, where it is captured by hemopexin (Hpx) and delivered in the form of the heme-hemopexin complex *via* the receptor CD91 to various sites in the body (Staroń et al. 2017; Tolosano and Altruda 2002).

Non-heme iron absorption occurs mainly in duodenal enterocytes. The first step in the transport of iron across the apical membrane of enterocytes is the reduction of ferric to ferrous ions, catalyzed by the membrane-associated ferrireductase duodenal cytochrome B (DcytB) (McKie et al. 2001). The low pH in the stomach and the presence of ascorbic acid (vitamin C) in the diet contribute significantly to reducing ferrous iron to ferric iron. (Gulec, Anderson, and Collins 2014). The ferrous iron is subsequently transported into the enterocyte *via* the divalent metal transporter 1 (DMT1)-dependent pathway at the apical membrane of the enterocytes (Gunshin et al. 1997). After crossing the apical membrane, iron enters LIP in the cytosol and is subsequently used for cellular needs, stored inside the cell in Ft, or exported into the circulation.

Ionic iron is exported from enterocytes by the only known mammalian iron transporter – ferroportin (Fpn) (Donovan et al. 2005) – which can be negatively regulated by the peptide hormone hepcidin (Drakesmith, Nemeth, and

Ganz 2015). The liver is the major source of circulating active hepcidin-25, which regulates systemic iron homeostasis. Hepatic hepcidin expression is regulated by a number of signals according to iron needs. The major hepcidin stimulators are iron itself, erythropoiesis, and inflammation. In contrast, iron deficiency inhibits hepcidin from restoring normal body iron levels by enhanced duodenal absorption and increased iron egress from the reticuloendothelial system (RES), mainly for the production of hemoglobin in erythroid cells. Iron export from enterocytes requires hephaestin (Heph), a ceruloplasmin homologue, a multicopper oxidase, which oxidizes ferrous ions to ferric ions prior to their binding by Tf in the blood (Vulpe et al. 1999). Iron in the complex with Tf is taken up by erythroblasts, hepatocytes, and other cells through transferrin receptor 1 (TfR1). It has been shown that TfR1 is more abundant in erythroblasts (the erythrocyte precursors in the bone marrow) than in any other cell types (Ponka and Lok 1999). TfR1 imports iron by internalizing the transferrin-iron complex through clathrin-mediated endocytosis. The Tf molecule, carrying one or two ferric ions, binds to TfR1 at the cell surface, initiating the internalization of the Tf/TfR1 complex into endosomes. The subsequent endosomal acidification and Fe^{3+} reduction by Steap 3 (Ohgami et al. 2005), endosomal ferrireductase causes Tf to release its ferric iron, which is then reduced to its ferrous form and is transported into the cytosol *via* DMT1 (Wang and Knutson 2013).

Iron recycling

Iron reutilization in the body is a complex process that ensures a daily iron supply for erythropoiesis. This process is based on the recycling of iron derived from senescent red blood cells (RBCs) by macrophages in the RES of the liver and spleen (Klei et al. 2017). The life span of an RBC is approximately 120 and 40 days in humans and mice, respectively. Over time, the plasma membrane undergoes harmful changes, the result of which is characteristic proteins and chemical compounds (aging markers) appearing on the cell membrane, making the cell susceptible to removal by macrophages. Macrophages engulf senescent RBCs in phagosomes and through erythrophagocytosis degrade the cellular compounds of the cells. After the breakdown of hemoglobin, heme released from this molecule is exported into the cytosol by the heme transporter, Hrg1 (White et al. 2013). In the cytosol, iron is extracted from the protoporphyrin ring by HO1 and is either stored in Ft or exported by Fpn cooperating with ceruloplasmin to the blood plasma and then mainly transported to the bone marrow, where it is used in erythropoiesis. Dietary iron absorption (2 mg of iron daily) itself cannot sustain erythropoiesis (which requires 20 mg of iron daily); thus, recycling of heme iron by HO1 (Kovtunovych et al. 2014; Starzyński et al. 2013) and its release by Fpn (Zhang et al. 2011) in macrophages are critical for satisfying the physiological iron needs for erythropoiesis.

Pathophysiology of iron

Iron deficiency manifests mainly as anemia. According to the World Health Organization (WHO 2017), anemia affects nearly one-third of the world's population, and 50% of anemia cases are attributed to iron deficiency. Iron deficiency may result from malnutrition, insufficient absorption of iron from the diet, malabsorption due to celiac disease, gastric or intestinal resection, Helicobacter pylori infection, increased blood loss due to menstruation, or iron loss associated with the development of parasites or peptic ulcer disease (Saboor et al. 2015). The increased need for iron during pregnancy associated with placental and fetal development may lead to anemia during pregnancy. Similarly, low iron supply and the huge need for iron ions associated with rapid postnatal growth can also cause iron deficiency anemia in newborns (Mazgaj et al. 2020; Szudzik et al. 2018). Both iron deficiencies are associated with a range of adverse outcomes in the offspring, including altered metabolism or cognitive and behavioral development (Gambling et al. 2002; Gambling et al. 2003). Another type of anemia characterized by functional iron deficiency (as opposed to true iron deficiency) is anemia of chronic disease, also known as anemia of inflammation. This kind of anemia is associated with several chronic diseases, such as autoimmune disorders, cancer, chronic kidney disease, inflammatory bowel diseases, and severe obesity (Camaschella 2017). In these disorders, inflammatory cytokines such as the interleukins IL-6 and IL-1 activate the JAK/STAT3 pathway to induce the transcription of hepcidin, which in turn downregulates Fpn and inhibits dietary iron absorption and iron recycling by macrophages. It is believed that hepcidin-induced inflammation has evolved to compete for iron from pathogenic microorganisms (for a comprehensive review see Wang and Babitt 2016). Some rare cases of anemia have been attributed to mutations in iron-related genes, including Tf (atransferrinemia), ceruloplasmin (aceruloplasminemia), and DMT1 (Camaschella 2017).

Conversely, systemic iron overloads occur in the case of HH, iron-loading anemias, and secondary iron overloads due to repetitive transfusions (Camaschella and Nai 2016). HH is caused by mutations in the gene-encoding hepcidin itself (HAMP) or by mutations in genes involved in regulating hepcidin expression in response to iron. Mutations in homeostatic iron regulator (HFE), transferrin receptor 2 (TFR2), or hemojuvelin (HJV) desensitize hepatocytes to detecting high iron levels, which leads to hepcidin downregulation (De Gobbi and Roetto 1993; Feder et al. 1996; Papanikolaou et al. 2004). Extremely low hepcidin levels result in high Fpn protein expression levels, and thus both unrestrained dietary iron absorption and macrophage iron recycling. A similar iron phenotype is caused by a missense mutation that converts alanine to aspartic acid at residue 77 (A77D) at the Fpn hepcidin-binding site. Partial loss of Fpn function leads to increased iron accumulation in tissue macrophages (Montosi et al. 2001).

Iron-loading anemias (thalassemias, congenital dyserythropoietic anemias, sideroblastic anemias, and myelodysplastic syndromes) are disorders caused by altered, ineffective erythropoiesis. In general, the expansion of immature erythroid precursors leads to the enhanced secretion of erythroid regulators (ERFE, GDF15, and TWSG1)

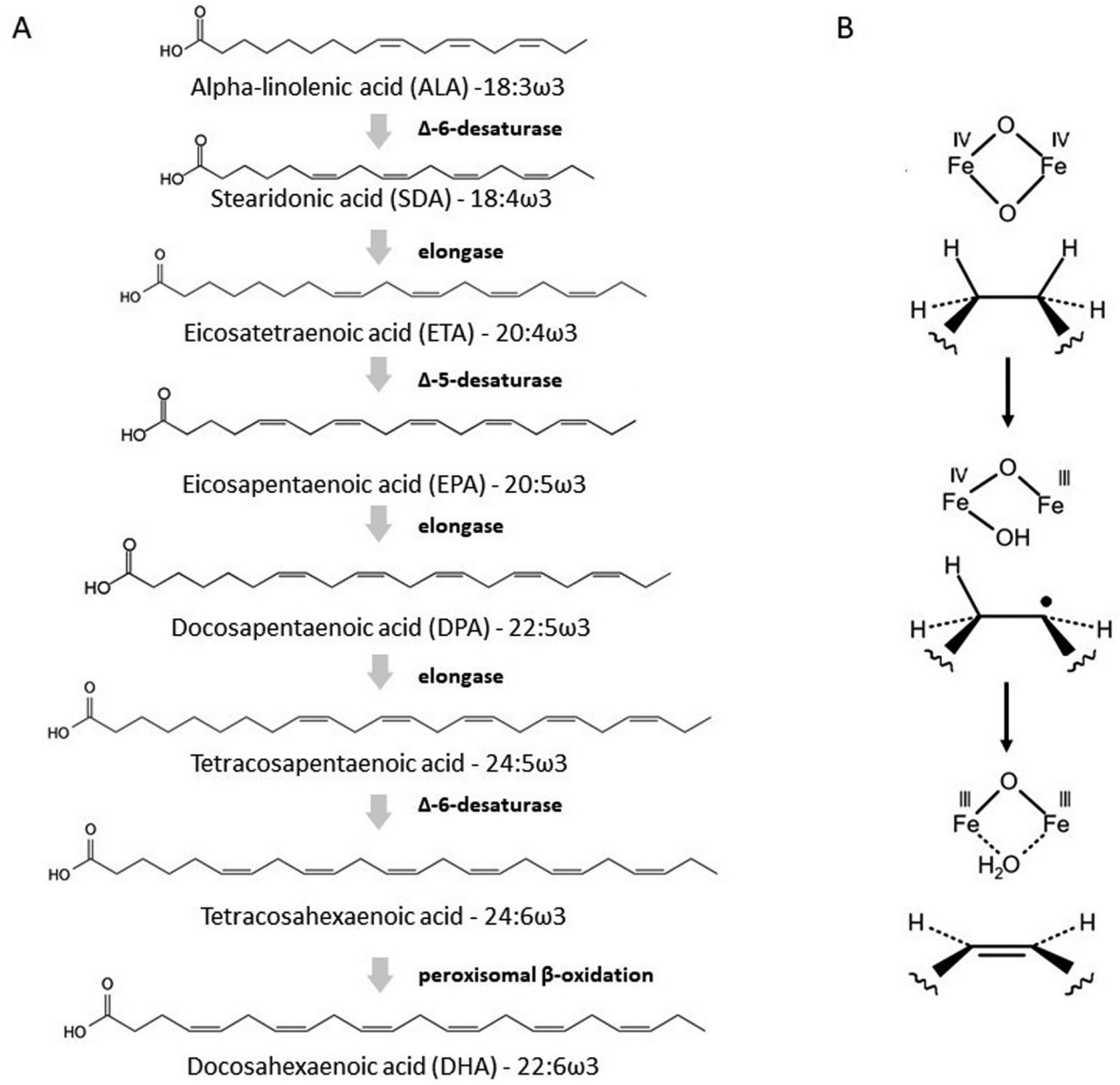

Figure 1. Desaturation and elongation of omega-3 fatty acids in the human body. (A) The essential dietary α-linolenic acid (ALA) is further processed in the endoplasmic reticulum into longer chain polyunsaturated fatty acids by a series of reactions catalyzed by the same set of enzymes, desaturase, and elongase. The final β-oxidation step takes place in peroxisomes. (B) The generally accepted mechanism for fatty acid desaturation. Fatty acid desaturases are nonheme diiron-containing enzymes. Iron catalytic core oxidizes unactivated C-H bonds. Desaturation is based on hydrogen atom abstraction, followed by production of carbon-centered radical that loses a second hydrogen to give an olefinic product (Buist 2004).

that suppress hepcidin expression. This suppression results in the dietary hyperabsorption of iron and secondary iron overload (Kim and Nemeth 2015). Moreover, patients with the above-mentioned syndromes require repetitive transfusions, which in turn potentiate iron loading. Transfusional iron overload is also common in dialyzed patients suffering from chronic kidney disease. They require blood transfusions due to blood losses from hemodialysis and have functional iron deficiencies due to anemia of inflammation (Honda et al. 2019).

In both HH and secondary iron overload syndromes, the iron exceeds the capacity of Tf to bind iron, leading to the appearance of highly reactive forms of NTBI. This plasma "free" iron is readily taken up by hepatocytes and other parenchymal tissues, including those of the heart, brain, and endocrine glands, where the excess iron intensifies oxidative damage and organ dysfunction. This oxidative cellular devastation is the etiology of several complications of hemochromatosis, such as progressive liver disease (fibrosis, cirrhosis, and hepatocellular cancer), diabetes, cardiomyopathy, hypogonadism, arthropathy, and osteoporosis (Pantopoulos 2018).

Omega-3 fatty acid metabolism

Fatty acids are a family of lipids that are generally aliphatic monocarboxylic acids. They can be classified into three diverse groups based upon the presence of double bonds within the aliphatic chain. A fatty acid is referred to as

saturated fatty acid (SFA) when it contains no double bonds. Conversely, monounsaturated fatty acids (MUFAs) contain one double bond, while fatty acids with two or more double bonds are termed polyunsaturated fatty acids (PUFAs) (Hulbert et al. 2005). Based on the location of the first cis double bond in the aliphatic chain, and counting carbon atoms from the methyl end of the fatty acid, PUFAs can be divided into three main families: omega-3, omega-6, and omega-9 fatty acids.

Fatty acids are delivered to the organism as triglycerides and phospholipids or free fatty acids. Before absorption in the small intestine, triglycerides and phospholipids have to be hydrolyzed by lipases. The absorption of the majority of the fatty acids occurs in the small intestine, where bile salts incorporate fatty acids and other fat digestion products into micelles. Then, the micelles are absorbed through enterocytes. The average absorption of ingested fat varies from 85% to 95% (Lichtenstein and Jones 2001). The concentration and composition of blood lipids depend on both the dietary intake and biotransformation of fatty acids. Hepatic fatty acid desaturation and elongation pathways are necessary, particularly when dietary long-chain fatty acids are inadequately supplied (Vessby et al. 2002).

Alpha-linolenic acid (ALA), which is an essential fatty acid, belongs to the omega-3 fatty acid family. It is indispensable for proper organism function; however, it cannot be synthesized *de novo* by humans or animals because of the lack of fatty acid omega-3 desaturase enzymes necessary to insert a *cis* double bond at the omega-3 position of a fatty acid. Other omega-3 fatty acids are delivered with food or are products of ALA elongation and desaturation (Figure 1). However, the rate of conversion is low. Healthy young men convert approximately 8% of dietary ALA to eicosapentaenoic acid (EPA) and up to 4% to docosahexaenoic acid (DHA) (Burdge, Jones, and Wootton 2002). The beneficial effects of both EPA and DHA on homeostasis and disease prevention have been widely studied.

Omega-3 fatty acids are essential for proper growth and development. Maintaining an optimal amount of and ratio between omega-3 fatty acids and other fatty acids in the diet helps prevent the development of diseases such as heart attacks, atherosclerosis, thrombosis, arrhythmia, stroke, immune-inflammatory disorders, asthma, arthritis, cancer, type II diabetes mellitus, obesity, and psychiatric disorders (Lands 2012). One of the main functions of fatty acids is supplying energy. Fatty acids are catabolized in the process of β-oxidation. In eukaryotes, it takes place in mitochondria. Acetyl-CoA, the β-oxidation product, enters the citric acid cycle in the respiratory chain taking part in ATP synthesis. Fatty acid catabolism provides significantly more energy than carbohydrate breakdown. Complete oxidation of 1 g of fatty acids provides 9 kcal (38 kJ), while in contrast, 1 g of carbohydrates or proteins provides only about 4 kcal (17 kJ) (Berg, Tymoczko, and Stryer 2002).

Omega-3 fatty acids are an inherent part of cell membranes. Depending on the type of fatty acid incorporated into the phospholipid layers, fatty acids modulate membrane properties, such as fluidity, flexibility, and permeability, as well as the activity of proteins submerged in the membrane (Stillwell and Wassall 2003). The organizational level of biological membranes depends on the length of the incorporated fatty acid chain and the degree of unsaturation. Compared to SFAs or MUFAs, PUFAs are considered highly disordered; therefore, their presence in membrane phospholipids leads to higher membrane flexibility (Gorjao et al. 2009). Furthermore, dietary omega-3 fatty acid intake strongly modulates the structure of membrane microdomains, called lipid rafts, which are enriched in glycosphingolipids and cholesterol. Lipid rafts function as centers for assembling cellular signaling molecules and trafficking. Unsaturated acyl chains, including omega-3 fatty acid chains, do not compact together with particles of cholesterol, which results in the formation of a disordered liquid phase, affecting cell membrane functioning (Edidin 2003). Due to the high conformational flexibility of omega-3 fatty acid acyl chains, they are able to affect the physical properties of the membrane, which can further modify protein functioning and trafficking, protein–protein interactions, vesicle budding, and fusion (Shaikh and Edidin 2006).

An important, positive effect of omega-3 fatty acids on body functioning is related to their antioxidant properties. In mouse tissues enriched with omega-3 fatty acids, H_2O_2 production was decreased (Hagopian et al. 2010). Furthermore, EPA or DHA can decrease the levels of ROS in cardiomyocytes treated with ROS-inducing drugs (Hsu, Chen, and Chen 2014). Moreover, Thorlaksdottir et al. (2006) revealed a positive correlation between RBC levels of omega-3 fatty acids and total plasma antioxidant capacity in humans. One of the mechanisms by which omega-3 fatty acids attenuate oxidative stress is the stabilization of nuclear factor erythroid 2-related factor 2 (Nrf2). Nrf2 initiates transcription of a number of genes encoding cytoprotective proteins, including superoxide dismutase (SOD), NAD(P)H quinone oxidoreductase 1 (Nqo1), glutamate-cysteine ligase catalytic subunit (Gclc), and HO1 (Gao et al. 2007). Several clinical studies have also revealed decreased levels of urinary and plasma F2 isoprostane, biomarkers of lipid peroxidation, in individuals supplemented with DHA and EPA (Giordano and Visioli 2014). Omega-3 fatty acids are also able to reduce lipoperoxidation levels, advanced glycation end products, and the superoxide dismutase/catalase (SOD/CAT) enzymatic ratio and increase SOD2 levels in the livers of diabetic rats (de Assis et al. 2012). On the other hand, PUFAs are more susceptible to oxidation than SFAs (Miller et al. 2013).

Omega-3 fatty acid derivatives serve as messenger molecules. They are involved in signal transduction in the nervous system and act as local hormones, stimulating and maintaining various actions in animal organisms, i.e., inflammation processes, regulation of blood supply to organs, and ion transport through membranes. Omega-3 fatty acids inhibit a number of aspects of inflammation, including leukocyte chemotaxis, adhesion molecule expression, and leukocyte-endothelial adhesive interactions (Calder 2017). They also play a crucial role in the metabolism of inflammatory and anti-inflammatory mediators. They attenuate production of arachidonic acid (AA)-derived proinflammatory eicosanoids, such as prostaglandin E2 (PGE2)

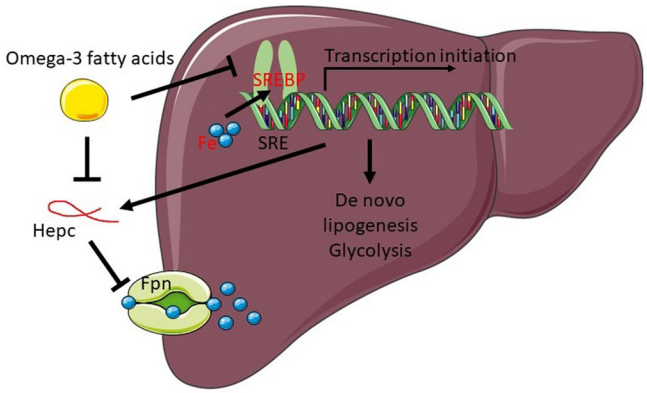

Figure 2. Sterol regulatory element-binding protein-1 (SREBP-1) transcription factor – a possible link between iron and omega-3 fatty acid metabolisms. SREBP seems to be important regulatory element in iron and omega-3 fatty acid interactions. Iron activates SREBP, which triggers the transcription of genes involved in fatty acid synthesis and glycolysis. Supplementation with iron leads to both a higher expression and DNA binding rate of SREBP. The mechanism of this regulation is unknown; however, the capacity of excessive iron to trigger oxidative stress may induce SREBP transcriptional activity (Sekiya et al. 2008). Moreover, SREBP activates the transcription of the *HAMP* gene and increases the blood plasma level of hepcidin (Hepc), which binds to ferroportin (Fpn), resulting in its degradation. Negative regulation of liver ferroportin leads to accumulation of iron in the liver. Omega-3 fatty acids exhibit an opposite effect, as they reduce the amount of SREBP and decrease hepcidin expression.

and leukotrienes (Peterson et al. 1998). EPA is also a substrate for the cyclooxygenase (COX), lipoxygenase (LOX), and cytochrome P450 enzymes that produce eicosanoids, largely prostaglandin E3 (PGE3). However, PGE3, compared to PGE2, exhibits lower potency toward the EP1, EP2, EP3, and EP4 receptors (Wada et al. 2007). Thus, EPA simultaneously decreases the levels of pro-inflammatory AA derivatives and prostaglandin products of effectively lower inflammatory potential. EPA and DHA also form endocannabinoids of anti-inflammatory properties – docosahexaenoyl ethanolamide and eicosapentaenoyl ethanolamide. Both decrease endotoxin-induced IL-6 synthesis, monocyte chemotactic protein (MCP1), and inducible nitric oxide synthase (Balvers et al. 2010; Meijerink et al. 2011). Omega-3 fatty acids are also the precursors of resolvins and protectins, which are enzymatically generated to orchestrate inflammation resolution (Levy 2010). Their anti-inflammatory effect is also strengthened by inhibiting the generation of cytokines, including tumor necrosis factor alpha (TNF-α), IL-1β, and IL-6 (Caughey et al. 1996; Meydani et al. 1991).

Interactions between omega-3 fatty acid and iron metabolisms

Liver

The liver, the largest body gland, is crucial for a number of physiological processes. It plays an essential role in carbohydrate, lipid, and protein metabolism; secretes bile; stores vitamins; synthesizes blood-clotting factors; filters blood; and removes redundant or toxic compounds. This organ may also play a pivotal role in the cross talk between iron and omega-3 fatty acids, as it is a place of synthesis and action of crucial enzymes involved in both metabolisms. The liver executes cholesterol synthesis and lipogenesis and produces triglycerides. Furthermore, a bulk of the body's lipoproteins is synthesized in this organ. Additionally, the liver is a major place of iron storage for Ft. It regulates iron recycling from senescent RBCs in the bloodstream by Browicz-Kupffer cells, a process controlled by hepcidin and largely synthesized in hepatocytes. Finally, the liver is the site of synthesis of other major proteins of iron metabolism, such as Tf and ceruloplasmin (Anderson and Shah 2013).

Recent studies have reported interactions between iron and omega-3 fatty acids, in which the liver plays a major role (Figure 2). Valenzuela et al. (2018) found that rats fed an iron-rich (200 mg iron/kg) diet for 21 days showed liver steatosis and augmented enhanced oxidative stress compared to rats fed a control diet (50 mg iron/kg). The excessive amount of delivered iron led to decreased activity of delta-5 and delta-6 desaturases, which are crucial enzymes for synthesizing long-chain omega-6 and omega-3 fatty acids. Indeed, the hepatic levels of PUFAs, including ALA, EPA, and DHA, were diminished. The loss of the aforementioned acids could be the effect of iron-induced oxidative stress and the high susceptibility of these PUFAs to oxygen radical-mediated oxidative damage (Videla and Pettinelli 2012). The reduced amount of PUFAs could be also the result of decreased activity of delta-5 and delta-6 desaturases, which are essential for their synthesis. Further, excessive iron caused higher expression and increased DNA binding of sterol regulatory element-binding protein-1c (SREBP-1c), while expression and DNA binding of peroxisome proliferator-activated receptor alpha (PPARα) were diminished. The key regulator of those transcriptional factors is omega-3 fatty acids. However, the effect of omega-3 fatty acids on PPARα and SREBP is opposite to the effect caused by iron. Omega-3 fatty acids activate PPARα, leading to reduced plasma lipids, to elevated fatty acid oxidation and anti-inflammatory effects, and to reduced liver steatosis. Simultaneously, they reduced the amount of mature SREBP-1, leading to inhibition of the downstream stimulatory effects of insulin, thereby reducing endogenous lipid production (Masterton, Plevris, and Hayes 2010). Similar results were obtained by Barrera et al. (2020), who tested rats under identical experimental conditions as those of Valenzuela et al. (2018). The animals fed an iron-rich diet were characterized by lower activity of delta-5 and delta-6 desaturases, lower levels of liver EPA and DHA, with a simultaneous increase in the omega-6/omega-3 long-chain PUFA (LCPUFA) ratio. The change in the LCPUFA ratio in the liver indicates that the iron-rich diet reduced the omega-3 fatty acid level more effectively than the omega-6 fatty acid level. Importantly, concomitant administration of antioxidant-rich olive oil abolished the aforementioned iron-induced changes in fatty acid metabolism and steatosis. Studies by Xiaoli, Song, and Yang (2019) have provided further knowledge about the role of SREBP in iron metabolism. The *Hamp* gene-encoding hepcidin has been found to be the target gene of the two SREBP isoforms, SREBP-1 a/c. In mice, overexpression of SREBP1-a increases hepatic hepcidin mRNA and the blood hepcidin level, reduces serum iron, increases hepatic iron storage, and leads to fatty liver. Human and animal studies

have indicated that oral administration of omega-3 fatty acids, unlike iron, decreases the level of hepcidin. In hemodialysis patients, daily consumption of 6 g flaxseed oil (containing mainly omega-3 ALA) for 8 weeks reduced serum hepcidin and improved RBC indices to a level comparable to that of the control group (Tabibi et al. 2017). Furthermore, the level of serum hepcidin was notably lower in obese children given a fish oil capsule containing 45 mg EPA and 225 mg DHA for eight weeks compared to others receiving a virgin coconut oil capsule (Sidiartha et al. 2017). Finally, diminished levels of hepcidin were observed in nephrectomized rats receiving 300 mg of omega-3 fatty acids per kg per day compared with non-supplemented rats (Lee et al. 2019). The mechanism of this phenomenon is unknown; however, a possible explanation may be related to the ability of omega-3 fatty acids to decrease the level of IL-6 (Ma et al. 2016), which has been shown to induce the expression of hepcidin (Nemeth et al. 2004). In contrast, no significant changes in serum hepcidin level were found in 110 pregnant women receiving a control diet or a diet supplemented daily with 400 mL of a drink containing 6.5% DHA, 6.5% EPA, and 37.1% total omega-3 fatty acids for 12 weeks. However, the serum hepcidin level in the umbilical cord artery was increased in the omega-3-supplemented group (Diaz-Castro et al. 2015).

There is also a supposed cross-link between omega-3 fatty acids and iron with regard to cholesterol metabolism. In mice, iron overload has been correlated with elevated hepatic cholesterol levels. This was associated with increased expression of seven genes involved in cholesterol biosynthesis: lathosterol oxidase (Scd5), 3-hydroxy-3-methylglutarate-CoA reductase (Hmgcr), lanosterol-14α demethylase (Cyp51), delta(14)-sterol reductase (Tm7sf2), sterol-4α-carboxylate-3-dehydrogenase (Nsdhl), cholestenol delta-isomerase (Ebp), and phosphomevalonate kinase (Pmvk) (Graham et al. 2010). Conversely, iron deficiency decreases serum cholesterol concentrations in humans and rats. Iron depletion leads to transcriptional upregulation of cholesterol 7 alpha-hydroxylase (Cyp7a1), sterol 12-alpha-hydroxylase (Cyp8b1), and cytochrome P450 oxidase (Cyp27a1) – bile acid synthetic enzymes – as well as to the induction of the Abcg5/8 cholesterol transporters in the rat liver. This results in the removal of cholesterol and the conversion to bile acid, through the reverse cholesterol transport mechanism (Prasnicka et al. 2017). In turn, omega-3 fatty acids decrease the level of plasma cholesterol in obese individuals (Kasbi Chadli et al. 2013). Dietary supplementation with omega-3 fatty acids has been reported to increase transcription of the *Cyp7a1* gene and the induction of bile acid synthesis. Such supplementation also induces Abcg5-mediated reverse cholesterol transport, by which excess cholesterol from peripheral tissues is transported back to the liver (Berard, Dumon, and Darmon 2004; Kasbi Chadli et al. 2013; Pizzini et al. 2017).

Growing evidence attests to the substantial role of both iron and omega-3 fatty acids in nonalcoholic fatty liver disease (NAFLD). Approximately every fourth person in the world suffers from NAFLD (Maurice and Manousou 2018). This disorder is characterized by unexplained pathological accumulation of fat in the liver that is not the outcome of any other disease (Masterton, Plevris, and Hayes 2010). A spectrum of lesions ranges from steatosis to a complex pattern of changes, including hepatocellular injury and damage caused by inflammation. In the coming years, NAFLD will become a major chronic liver disease in adults and children and could become the leading indication for liver transplantation (Neuschwander-Tetri 2017). Its pathogenesis is still not fully understood. It is assumed to be the outcome of steatosis, mainly through triglyceride accumulation and irregularities in insulin metabolism, as these are the first symptoms to appear (Masterton, Plevris, and Hayes 2010). However, it seems to be a more complex process including *inter alia* lipotoxicity, insulin resistance, oxidative stress, and inflammatory cascade. An important aspect in the development of the disease is disrupted iron metabolism, as approximately one-third of patients with NAFLD show elevated serum Ft and hepatic iron overload (Nelson, Klintworth, and Kowdley 2012). Importantly, the omega-3 fatty acid level is decreased in the livers of patients with NAFLD (Puri et al. 2007).

A pathogenic accumulation of lipids in the liver is the key feature of NAFLD. Inhibition of this process is one of the main areas of focus in developing therapies against the disease. Omega-3 fatty acids are key regulators of transcription of hepatic genes involved in lipid metabolism. They are ligands for PPARα, the activation of which promotes catabolism of fatty acids. The lack of PPARα in hepatocytes promotes NAFLD and liver inflammation in mice fed a high-fat diet (Regnier et al. 2020). Simultaneously, omega-3 fatty acids inhibit SREBP, leading to the attenuation of *de novo* lipogenesis. As mentioned above, iron acts oppositely, as it stimulates the activation of SREBP (Valenzuela et al. 2018). The main enzyme responsible for fatty acid synthesis and the successive formation of triacylglycerols (a major marker of NAFLD) is stearoyl-CoA desaturase (SCD). Its transcription is positively regulated by SREBP. Omega-3 fatty acids counteract hepatic steatosis in rats through depletion of SCD (McNamara et al. 2012). In contrast, a cross-sectional study of 447 women noted an association between elevated serum Ft level and SCD activity (Wu, Baylin, and Colacino 2018). This finding is in line with studies performed on mice, which revealed increased expression and activity of SCD in the liver during iron overload (Pigeon et al. 2001). Hepatic lipid accumulation induces also endoplasmic reticulum stress which in turn up-regulates hepcidin through two complementary mechanisms (Belot et al. 2020). The first involves the inhibition of matriptase-2, which activates Bmp-Smad signaling pathway necessary for the induction of hepcidin. The second is based on the stabilization of hepcidin mRNA by the RNA-binding protein – HuR. Up-regulation of hepcidin leads to hepatic iron accumulation, a poor prognosis factor for patients with NAFLD.

The development of NAFLD is influenced by multiple environmental and genetic factors. One factor playing a major role is oxidative stress. Turnover of hepatic lipid stores results in triglyceride catabolism and non-esterified fatty acid mobilization from adipose depots, and therefore enhanced β-oxidation. In NAFLD, the capacity of mitochondria to β-oxidize fatty acids is overload, which results in

incomplete fatty acid oxidation and uncoupled mitochondrial respiration. Abnormalities in mitochondrial respiration generate ROS. In liver containing high levels of lipids, ROS induce lipid peroxidation, which intensifies the respiratory chain and mitochondrial genome oxidative damage, leading to the exacerbation of the disease (Jump et al. 2018). High hepatic iron levels, a hallmark of NAFLD, initiate an oxidative stress cascade, leading to lipid peroxidation and mitochondrial dysfunction (Nelson, Klintworth, and Kowdley 2012). Furthermore, iron-induced ROS and nitrogen species lead to the increased production of pro-inflammatory cytokines and fibrogenic response (Britton, Subramaniam, and Crawford 2016). The diminished oxidative stress has been observed in the liver of rats subjected to phlebotomy or fed an iron-deficient diet (Minamiyama et al. 2010). In NAFLD patients, increased lipid peroxidation was shown to be related to elevated hepatic iron stores (MacDonald et al. 2001). Also, the rate of oxidative damage to DNA in the liver was positively correlated with iron overload in nonalcoholic steatohepatitis (Fujita et al. 2009). Increased oxidative stress in NAFLD contributes to steatosis due to higher peroxidation and defective fatty acid desaturation of omega-3 fatty acids, which counteract disease progression (Videla et al. 2004).

Oxidative stress also increases the levels of nuclear SREBP and lipid accumulation in cultured hepatocytes (Sekiya et al. 2008). The level of sirtuin 1 (SIRT1) and CycC/CDK, negative regulators of SREBP, is diminished by oxidative stress (Cooper et al. 2012; Salminen, Kaarniranta, and Kauppinen 2013). Indeed, lower abundance of the CycC/CDK complex in mouse models of NAFLD leads to higher level of SREBP-1c and therefore to a higher level of *de novo* lipogenesis (Feng et al. 2015). The same effect has been observed for SIRT1. Increased expression of SIRT1 leads to deacetylation and inhibition of SREB1-c, a regulation correlated with the reduction in hepatic steatosis (Ponugoti et al. 2010). In this context, the triggering effect of iron and the inhibitory effect of omega-3 fatty acids on the SREBP transcription factor described above seem to be significant.

By downregulating phosphatase activity, ROS activate nuclear factor kappa B (NF-κB), a transcription factor regulating inflammation and cell death that plays a major role in the development of hepatocellular injury and liver fibrosis in NAFLD. Omega-3 fatty acid supplementation protects the liver from injury through PPAR-α's antagonistic effect against NF-κB-controlled transcription of pro-inflammatory mediators, including TNF-α and IL-1β, leading to the reestablishment of inflammatory cytokine homeostasis (Zuniga et al. 2011). On the other hand, iron-induced ROS and nitrogen species activate the NF-κB, leading to the enhancement of TNF-α-dependent liver injury (Chen et al. 2007; She et al. 2002). Interestingly, activation of the TLR4/NF-κB pathway induces the expression of hepcidin, which may explain the accumulation of excess iron in the liver and the further progression of pathological hepatic changes (Chen et al. 2016).

Central nervous system

Iron and brain lipids

In recent years, there have been considerable new insights into iron homeostasis in the brain, as well as the mechanisms of its dysregulation in neurodegenerative diseases associated with oxidative stress (Devos et al. 2020). The brain is an iron-rich organ. In some regions of the brain, such as the substantia nigra, pars compacta, or basal ganglia, the iron concentration is comparable to that found in the liver (Drayer 1988; Haacke et al. 2005; Singh et al. 2014). The brain needs considerable amounts of iron, as it is indispensable for many biological processes occurring in neuronal tissue, such as high-intensity metabolic and energetic processes, as well as myelin and neurotransmitter synthesis (Thirupathi and Chang 2019). It is well known that excessive iron accumulation occurs during aging in healthy individuals and to a major extent in patients with neurodegenerative diseases, such as neurodegeneration with brain iron accumulation (NBIA) diseases (Kurian et al. 2011), Alzheimer's (Connor et al. 1992), Parkinson's (Sofic et al. 1988), Huntington's (Agrawal et al. 2018), amyotrophic lateral sclerosis (ALS) (Bu, Xiang, and Guo 2019), and even prion disease (Ashok and Singh 2018). However, due to disagreements among researchers regarding whether iron accumulation in the brain is a primary or secondary event of neurodegeneration, the contribution of iron to the pathogenesis of neurodegenerative disorders has often been neglected.

In contrast, much less is known about the role of iron deficiency in the development of brain disorders in infancy and function later in life, which do not disappear even after iron supplementation later in life (Lozoff and Georgieff 2006). For schoolchildren, the most significant neurological signs that iron deficiency occurred in infancy include learning difficulties, reduced cognitive skills, and educational problems (Oski et al. 1983). It is believed that hypomyelination – disruption of the myelination process, i.e., the production of the myelin sheath around nerve fibers in the brain and medulla oblongata – is the basis of these phenomena (Oski et al. 1983).

Central nervous system iron metabolism: an overview

Delivery of iron to the central nervous system (CNS) requires penetrating one of two cellular barriers: the blood–brain barrier (BBB) or the blood–cerebrospinal fluid barrier (BCSFB) (Rouault 2009). The BBB is formed by tightly adherent, polarized brain capillary endothelial cells (BCECs). At the apical site (luminal membrane), cell membranes come into contact with blood and with interstitial fluid at the basolateral site (abluminal membrane). At the CNS side, the BBB is made of astrocytes, the largest glial cells that make contact with BCECs using the so-called endfeet (McCarthy and Kosman 2015). The BCSFB is present in the choroid plexus, a structure that produces cerebrospinal fluid, and in contrast to vascular endothelial cells within the BBB, endothelial cells of the choroid plexus are separated (fenestration), which allows free transport from the bloodstream. The proper cell barriers in the choroid plexus are ependymocytes, covering the walls of the brain ventricles, as well as the central canal of the spinal cord; ependymocytes are a

type of glial cell containing numerous microvilli facing the lumen of the cerebral ventricles. Similar to other cell types, iron transport into the brain through the BBB starts by binding the circulating Tf to TfR1 at the apical membrane of BCECs (Crichton and Ward 1992). Two models of iron transport across BCECs are postulated. First, an older hypothesis assumes that in the absence of DMT1 in BCECs, TfR1 is a cargo protein for iron delivered to astrocytes. Based on this model, endosomes pass through the cytosol of the BCECs to be released into the brain at the abluminal membrane of BCECs. Then, the metal is bound to low-molecular-weight compounds such as citrate, ATP, or ascorbate (Moos et al. 2007). The release of low-molecular-weight compounds by astrocytes into the extracellular environment promotes the formation of the pool of NTBI in the brain. Although NTBI may be a major form of iron imported by astrocytes in vivo, the mechanisms responsible remain unclear. There is evidence that ascorbate is intimately involved in iron accumulation by astrocytes and is thus an important contributor to iron homoeostasis in the mammalian brain (Lane et al. 2010). Second, the canonical receptor-mediated endocytosis model, based on the internalization of the Tf-TfR1 complex, assumes that the iron released from the endosomal Tf-TfR1 complex after prior acidification of the endosome is released from Tf, reduced to iron, and exported to cytosol or stored in Ft. Iron is then exported to the brain by Fpn (Wu et al. 2004). Iron uptake by astrocytes is also not clear, considering that these cells do not express TfR1 and apart from NTBI absorption, possibly taking up iron *via* DMT1 or other unknown transporters. The location of the astrocytes predisposes these cells distribute iron to other cells in the CNS. It is well documented that astrocytes highly express two molecules anchored in the plasma membrane that are involved in iron export: Fpn and ceruloplasmin (Wong and Duce 2014; Wong et al. 2014). Interestingly, there is evidence that ceruloplasmin jointly with Heph may act in the brain and kidney in releasing iron from the cells (Jiang et al. 2016; Jiang et al. 2015). The iron not stored in Ft is exported from the astrocytes and inserted into the extracellular Tf, which is secreted from the choroid plexus. Interestingly, Tf saturation in the CNS of healthy subjects is extremely high, comparable to the plasma Tf saturation in hemochromatosis (Moos et al. 2007). It is believed that astrocytes redistribute iron in the brain and that Tf is the major iron transport protein in the brain, taken up by neurons through TfR1-mediated endocytosis. Iron export from neurons is possible and carried out by Fpn in cooperation with the so-called soluble ceruloplasmin. Interestingly, the pathological hallmarks of Alzheimer's disease are the accumulation of extracellular amyloid plaques seeded by aggregated amyloid beta peptide (Aβ) and intracellular neurofibrillary tangles composed of hyperphosphorylated microtubule-associated protein tau. Iron efflux associated with Fpn stabilization on the plasma membrane by amyloid precursor protein, which is transported to the membrane by the microtubule-associated protein tau, has been reported. Iron-induced tau hyperphosphorylation and its aggregation are considered iron-related etiology of Alzheimer's disease (Ayton, Lei, and Bush 2013). Moreover, tau accumulation in neurofibrillary tangles is associated with an induction of heme oxygenase-1, which can exacerbate oxidative stress through the release of iron by the breakdown of heme. Within the brain, oligodendrocytes are cells that exhibit profound iron and Ft staining and are involved in myelinization (Connor et al. 1994). Interestingly, mature oligodendrocytes do not express TfR1 (Han et al. 2003); thus, the question of how this metal is imported into these cells remains open. A partial explanation of this phenomenon is the observation that in ontogeny, saturated Ft appears first in microglia and then in mature oligodendrocytes (Connor et al. 1994), suggesting that Ft is a cargo protein that transfers iron between cells. Whether Ft is released from microglia remains unresolved. Interestingly, T cell immunoglobin mucin domain 2 (Tim2) protein receptors have been identified, suggesting iron transport in the form of Ft in rodent oligodendrocytes (Todorich, Zhang, and Connor 2011; Todorich et al. 2008). Recent evidence has shown that brain microglia preferentially acquire iron from Tf or from non-Tf sources, depending on their polarization state. Thus, NTBI uptake is enhanced by the pro-inflammatory response (to lipopolysaccharide or β-amyloid) and under these conditions, microglia sequester both extra- and intracellular iron (McCarthy et al. 2018).

The role of the choroid plexus as a structure participating in iron transport from the circulation to CNS was initially underestimated, mainly due to the low absorptive surface of this brain structure, which was estimated at about 50% of the BBB. However, due to the presence of microvilli at the ependymocytes' surface and higher blood flow through the choroid plexus vessels, iron transport to the CNS *via* BCSFB is considered significant (Keep and Jones 1990). In situ hybridization analysis in the choroid plexus has revealed a complete set of proteins potentially active in iron transport and characteristic of bipolar cells: TfR1, DMT1, Fpn, ceruloplasmin, Heph, and Dcytb (Rouault and Cooperman 2006).

Brain iron homeostasis seems to be relatively independent of systemic iron metabolism but some experimental evidence show little effect on brain iron metabolism driven by systemic plasma hepcidin, which is synthetized by hepatocytes (Belaidi and Bush 2016). Rodent models show that liver hepcidin has important consequences in brain pathologies, such as brain hemorrhage/ischemia. During brain hemorrhage/ischemia liver hepcidin is upregulated, which is accompanied with increased brain iron content (Xiong et al. 2016). Importantly, hepcidin knockout decreases brain iron level in models with brain hemorrhage, but not in physiological conditions (Tan et al. 2016; Xiong et al. 2016). But on the other hand, there are a solid data showing local brain hepcidin expression (Wang et al. 2008; Raha et al. 2013), which may explain independence of central nervous system iron homeostasis.

Omega-3 fatty acids and the brain

Of the organs of the body, the brain is one of the most abundant in terms of lipid content. The primary role of lipids is membrane formation. The human brain consists of

60% lipids, mostly glycerophospholipids and sphingolipids, as well as a great pool of cholesterol and cholesterol metabolites. One-third of phospholipids are PUFA derivatives (Czyż et al. 2016). White matter contains mostly MUFAs, while gray matter encompasses mostly PUFAs. The most abundant PUFA in the brain are AA and DHA, accounting for about one fifth of the brain's dry weight. Brain EPA levels are limited and are typically 250–300 times lower than DHA levels (Chen et al. 2009). Brain cells – neurons, glial cells, and mainly astrocytes and oligodendrocytes – contain very high levels of AA and DHA. However, it should be noted that these compounds are not present in sufficient quantities in modern diets (Bourre et al. 1989). This deficiency is of crucial importance, as the endogenous synthesis of EPA and DHA in the brain is too low and must be supported by uptake from the unesterified fatty acid pool of plasma (Demar et al. 2005). Therefore, it has been suggested that the brain maintains its omega-3 fatty acid levels mainly *via* uptake from dietary and/or liver sources in plasma (Dyall 2015). EPA and DHA were shown to enter the brain at similar rates and cross the BBB by simple diffusion (Ouellet et al. 2009). The phospholipid location of omega-3 fatty acids differs within the brain. DHA is predominantly abundant in phosphatidylethanolamine and phosphatidylserine, whereas EPA appears in phosphatidylinositol (Chen et al. 2009). Both omega-3 and omega-6 fatty acids are esterified in the sn-2 position into phospholipids and play critical structural and functional roles in the cell membranes of the brain. The fatty acid composition strongly affects the content and arrangement of membranes and therefore influences their fluidity. The presence of PUFAs in membrane bilayers lowers their melting point (Bentsen 2017). Phospholipids made from a PUFA are also more fluid than those that incorporate SFAs. In addition, omega-3 ALA has some effect *per se* on the neuronal membrane fluidity index. It is able to decrease the cholesterol level in the neuronal membrane, which would otherwise decrease membrane fluidity, which in turn would disturb cell homeostasis and increase the cell's susceptibility to injury and death (Yehuda et al. 2002). Additionally, the presence of omega-3 fatty acids affects brain functioning by modulating the activity of membrane-bound enzymes, as well as the number and affinity of receptors and the function of ion channels. Moreover, omega-3 fatty acids may influence the production and activity of neurotransmitters and signal transduction, which controls the activity of neurotransmitters and neuronal growth factors (Yehuda, Rabinovitz, and Mostofsky 2005). An important feature of PUFAs is that they are more susceptible to oxidation compared to SFAs and MUFAs. This leads to the PUFA-rich brain membrane structure being especially sensitive to reactive oxygen and nitrogen species under oxidative stress conditions.

The balance between free-form PUFAs also has special significance in neuroinflammation. PUFAs and their derivatives are involved in regulating microglia and controlling neuroinflammation, where AA derivatives generally display pro-inflammatory activities, while DHA derivatives are anti-inflammatory and pro-resolving (Laye et al. 2018).

Fatty acids from food are of crucial importance for the brain's fatty acid composition. An additional factor is age, as in older individuals, the content of PUFAs in the brain decreases in favor of other fatty acids. Furthermore, several human and rodent studies have suggested that PUFA levels vary with gender, i.e., they are higher in females than in males (Lin et al. 2016). Supplementation with PUFAs and vitamin E is positively correlated with fractional anisotropy, which corresponds to improved white matter integrity (Gu et al. 2016). Also, the consumption of fish rich in EPA and DHA (Raji et al. 2014) and higher blood levels of EPA and DHA (Samieri et al. 2012) lead to improved gray matter volume in several brain regions. Studies with older individuals have produced interesting results regarding their brain remodeling and cognitive functions. Participants consumed fish oil, containing 2.2 g of omega-3 fatty acids daily, or a placebo for 26 weeks. The fish oil supplementation resulted in better structural integrity of white and gray matter and amelioration of executive function and verbal fluency scores (Witte et al. 2014).

Iron and PUFAs in ferroptosis

As mentioned in the introduction, iron participating in the Fenton reaction generates ROS, which in turn produce oxidized lipid-derived compounds, i.e., lipid hydroperoxides (Meneghini 1997). Lipid peroxidation has been widely observed in neurodegenerative diseases and has also been connected with tissular iron deposits and cell death (Stockwell et al. 2017; Weiland et al. 2019). The mechanism by which cells die through the interaction between ROS and iron has been widely investigated and is termed ferroptosis (Dixon et al. 2012). Ferroptosis is a form of regulated cell death characterized by the iron-dependent accumulation of lipid hydroperoxides to lethal levels. So far, ferroptosis has been implicated in the pathological cell death associated with degenerative diseases (i.e., Alzheimer's, Huntington's, and Parkinson's diseases), carcinogenesis, stroke, intracerebral hemorrhage, traumatic brain injury, and others (Magtanong and Dixon 2018; Xie et al. 2016). Unlike other programmed cell deaths such as apoptosis, necroptosis, and autophagy, cell death by ferroptosis is manifested without involvement of caspases, Bcl-2 homologous antagonist killer (BAK), or Bcl-2-associated X protein (BAX). In this process, cells are intact, devoid of blebbing, and show unnoticeable chromatin condensation (Latunde-Dada 2017). In general, the interplay between iron and lipids during ferroptosis is characterized by ROS accumulation due to increased LIP levels and in turn due to massive lipid peroxidation, which may perturb cellular membrane transport or mitochondrial function. It was well documented that decreased cellular capacity to reduce ROS increases the level of lipid peroxides and that this is the signal that triggers ferroptosis. Conditional disruption of glutathione peroxidase 4 (GPX4), an enzyme that neutralizes lipid peroxides and ensures membrane fluidity, clearly indicates that PUFAs are the primary source of lipid peroxides (Seiler et al. 2008) through the action of lipoxygenases. Moreover, PUFAs have been shown to be the lipids most susceptible to peroxidation in

the course of ferroptosis and that the prevention of this peroxidation by supplementing cells with PUFAs deuterated at the susceptible bis-allyclic carbon suppresses ferroptosis. PUFAs containing the heavy hydrogen isotope deuterium at the site of peroxidation (D-PUFA) prevent PUFA oxidation and block ferroptosis. This study also led to the identification of lipoxygenases and phosphorylase kinase catalytic subunit gamma 2 (PHKG2) as regulators of PUFA peroxidation during ferroptosis. D-PUFAs have been demonstrated to have therapeutic efficacy in several human disease models, including Parkinson's disease (Shchepinov et al. 2011) and Friedreich's ataxia (Cotticelli et al. 2013). Strong and specific suppression of ferroptosis by D-PUFAs suggests the possible involvement of ferroptosis in such diseases and supports the idea of using ferroptosis inhibitors to delay disease progression. This is also the argument for assuming that other NBIA diseases might be associated with ferroptosis. For instance, ferroptosis inhibited by GPX4 provides a protective mechanism against neurodegeneration (Cardoso et al. 2017). What is more, GPX4 and ferroptosis are postulated to play a major role in the development of nonalcoholic steatohepatitis (NASH) (Qi et al. 2020). Thus, triggering or inhibiting ferroptosis might present a novel therapeutic strategy for cancer and neuronal and hepatic diseases. Relevant to this, it is intriguing that oleic acid, a MUFA, strongly rescued cells from ferroptosis. Treatment with oleic acid might decrease the abundance of PUFAs in the cell membrane or activate a downstream signaling pathway to exert an indirect antioxidant effect.

Undeniably, PUFAs play important role in ferroptosis, although there are still too few reports that categorize the effects of omega-6 vs. omega-3 fatty acids in this process. It is evident that both omega-6 and omega-3 fatty acids are characterized by their higher susceptibility to oxidation compared to SFAs and MUFAs; therefore, they may promote ferroptosis. However, phosphatidylethanolamine (PE), which contains the omega-6 fatty acid AA or its derivative adrenaline, turned out to be a key phospholipid that induces ferroptosis in cells. Also eicosatetraenoyl-phosphatidylethanolamine (ETE-PE), AA derivative, exhibits remarkable selectivity toward peroxidation comparing to other of polyunsaturated fatty acyl-phospholipids (PUFA-PLs) (Anthonymuthu et al. 2020). Inhibition of acyl-CoA synthetase long-chain family member 4 (ACSL4) and lysophosphatidylcholine acyltransferase 3 (LPCAT3), which participate in the biosynthesis of PE and exhibit a preference toward AA, counteracts the accumulation of lipid peroxide substrates in cells, thus inhibiting ferroptosis (Kagan et al. 2017). What is more dietary delivery of dihomogamma-linolenic omega-6 fatty acid (DGLA) was proven to trigger germ-cell ferroptosis in *Caenorhabditis elegans* (Perez et al. 2020). On the other hand, the omega-3 fatty acid DHA added to a murine hippocampal cell line induces the remodeling of membrane phospholipids and upregulates GPX4 expression, triggering a transcriptional program to increase the expression of members of the glutathione and thioredoxin systems, the key enzymes providing neuronal protection (Casanas-Sanchez et al. 2014). Therefore, omega-3 fatty acids may act as a double-edged sword in ferroptosis. The evidence of the exact role of PUFAs in ferroptosis in the brain requires further study, especially to discriminate between the contributions of omega-6 and omega-3 fatty acids in this process.

Interestingly, a recent discovery showed that autophagy contributes to ferroptosis by degrading Ft in fibroblasts and cancer cells, in a process called ferritinophagy (Hou et al. 2016). Knockout or knockdown of autophagy-related genes (Atg5 and Atg7) limited erastin-induced ferroptosis with decreased intracellular ferrous iron levels, as well as lipid peroxidation. Remarkably, nuclear receptor coactivator 4 (NCOA4) was shown to be a cargo receptor for the selective autophagic turnover of Ft in the process of ferroptosis. Genetic inhibition of NCOA4 stopped both Ft degradation and ferroptosis. NCOA4 overexpression induced Ft degradation, increased iron levels, and promoted ferroptosis. These findings showed a new role for Ft as the donor of free iron in the process of ferritinophagy. The autophagic degradation of Ft protein might be an important ferroptosis process in the CNS.

Iron and PUFAs in immunity

It is well established that both iron and PUFAs are important for immune function (Darwesh et al. 2019; Ekiz et al. 2005). Iron deficiency impairs lymphocyte proliferation and affects B cell function (Beard 2001), whereas availability of PUFAs might change the fatty acid composition of the phospholipid membranes of lymphocytes and monocytes (Barros et al. 2013). However, only a few studies have shown direct evidence of iron–PUFA interaction in terms of immune response. Iron enters the catalytic center of desaturase enzymes, which are responsible for the conversion of ALA into EPA and DHA. Therefore, iron deficiency can alter immune defense by decreasing the amount of generated EPA and DHA-derived mediators with anti-inflammatory properties (Nakamura and Nara 2004). Moreover, iron is a co-factor of lipoxygenase and cyclooxygenase, which are both involved in the synthesis of eicosanoids derived from PUFAs (Boutaud and Brash 1999). Therefore, nutritional deficiency of both iron and PUFAs may affect one another, which can increase or decrease the effects of each deficiency. In some cases, iron deficiency must be treated by iron supplementation, which in turn can favor infections with some strains of bacteria (Jaeggi et al. 2015), and this could even be lethal in some cases (Sazawal et al. 2006). Some two-by-two double-blind randomized trials have shown that an 8.5-month iron supplementation (50 mg per day) increased respiratory morbidity in 6- to 11-year-old South African children. However, the combination of iron supplementation with 420 mg of DHA and 80 mg of EPA per day prevented this increase in respiratory morbidity (Malan et al. 2015). The same authors examined the biochemical effects of iron and a mixture of the two bioactive omega-3 PUFAs – DHA and EPA – alone and in combination. They analyzed changes in plasma lipid-derived immune mediator concentrations and the expression of genes involved in their synthesis, as well as antioxidative and iron regulatory gene expression in peripheral blood mononuclear cells (Malan et al. 2016). They showed for the first time that DHA/EPA supplementation altered the profile of the lipid-derived

immune modulators to being more anti-inflammatory or pro-resolving. It also decreased the pro-inflammatory hydroxyeicosatetraenoic acid (12-HETE) and tended to increase the pro-resolving 17S-hydroxy-DHA (17-HDHA). 12-HETE has been shown to be involved in inflammatory processes and oxidative stress, and has been associated with cardiovascular disease, diabetes, and hypertension. In contrast, the anti-inflammatory D-series resolvins produced from 17-HDHA have been demonstrated to activate several mechanisms aimed at resolving localized inflammation (Malan et al. 2016). It has been shown that patients suffering from both Alzheimer's disease and type 2 diabetes mellitus are characterized by brain inflammation (De Felice, Lourenco, and Ferreira 2014) due to hyperglycemia. It is also well known that under inflammatory conditions, omega-3 fatty acids may act as anti-inflammatory agents. Unexpectedly, recent data using a rat model of type 2 diabetes mellitus suggest that upon iron supplementation, omega-3 fatty acids lose their antioxidant properties in the hippocampus due to lipid peroxidation (Gholamhosseinian et al. 2020). In conclusion, all three of these studies clearly suggest a biologically important interaction between iron and omega-3 fatty acids in immunity.

Iron and PUFAs in cognition

As mentioned above, PUFAs present in high concentrations in the brain tissue are a natural target for ROS-mediated lipid peroxidation (Rice-Evans and Burdon 1993). In addition, brain tissues have high energy requirements and consequently, high oxygen demand, 2%–3% of which is transformed into ROS. Data showing iron-induced oxidative stress cell death in vitro demonstrated a rapid (30-minute) translocation of ethanolamine phosphoglyceride and serine phosphoglyceride, changing the topology of the plasma membranes of oligodendroglia-like cell line (OLN 93) following three days of supplementation of DHA (Brand and Yavin 2001, 2005). These authors, using OLN 93 and PC12 cells, concluded that the accumulation of intracellular iron modulated by DHA supplements is associated with enhanced iron import and a significant increase in DMT1 gene expression (Brand et al. 2008; Schonfeld et al. 2007). Moreover, these effects were specific to cells enriched with DHA. Of note, AA supplements did not induce any changes. Similarly, TfR1 was significantly elevated following DHA and AA supplementation. This in vitro finding based on neuronal cellular models may have important implications for understanding the interactive role of iron and PUFAs in excessive iron accumulation in degenerative disorders, but primarily in nutritional deficiencies, such as PUFA losses in the aging brain (Freemantle et al. 2006), iron deficiency in childhood, or their interaction/interplay.

The impact of iron deficiency on cognition during pregnancy and early postnatal life has been extensively studied in humans and animal models of iron deficiency (Berard, Dumon, and Darmon 2004; Lipinski, Stys, and Starzynski 2013). It is well established that iron deficiency in childhood, especially during the first five years of life, alters neurotransmitter homeostasis and impairs synaptogenesis and the conduction of impulses in the brain. Iron deficiency also reduces the metabolism of monoamine and brain hypomyelination by impairing the oligodendrocyte synthesis of lipids and cholesterol in oligodendrocytes (Beard 2003; Beard and Connor 2003; Kim and Wessling-Resnick 2014; Todorich et al. 2008). These pathological conditions in the brain during postnatal development show a link between iron deficiency or anemia in children and impaired psychomotor development (Pala et al. 2010; Walter 2003), as well as impaired cognitive functions, such as concentration, intellectual status, memory, and learning skills (Falkingham et al. 2010; Soemantri, Pollitt, and Kim 1985). Interestingly, recent studies have investigated the relationship between iron deficiency and attention-deficit/hyperactivity disorder (ADHD) and autism spectrum disorder, two of the most common neurobehavioral disorders in children (Herguner et al. 2012; Tseng et al. 2018). Associations between ADHD and lower serum Ft levels, as well as iron deficiency were found (for a comprehensive review, see Pivina et al. 2019).

Early studies by Baumgartner and coworkers have allowed scientists to link iron metabolism with omega-3 fatty acid levels in the context of cognition in rats and humans. The authors showed additive and interactive effects of concurrent iron deficiency and essential ALA fatty acids on brain monoamine concentrations and on spatial working and reference memory in young (5-week-old) rats (Baumgartner et al. 2012a). Other brain neurotransmitter systems, which can regulate memory and behavior, have not been considered. To determine whether these effects are lasting or can be reversed by repletion with iron and omega-3 fatty acids, rats with concurrent iron deficiency and omega-3 fatty acids were given iron and DHA/EPA, alone and in combination (Baumgartner et al. 2012a). The provision of iron in combination with DHA/EPA synergistically increased iron concentrations in the olfactory bulb, probably due to increased DMT1 expression, as mentioned before. Supplementation with DHA/EPA in combination with iron resulted in higher brain DHA concentrations than DHA alone in the frontal cortex and olfactory bulb. Moreover, supplementation with DHA/EPA in combination with iron upregulated the hippocampal dopamine receptor D1, and a significant synergistic effect of iron and DHA/EPA on serotonin levels was detected. Working memory performance was impaired in iron-deficient DHA/EPA rats compared with controls. In the reference memory task, adding iron/DHA/EPA improved learning behavior, but iron or DHA/EPA alone did not. These findings suggest that feeding either iron or DHA/EPA alone to adult rats with both iron deficiency and omega-3 fatty acids affects the dopamine and serotonin pathways differently than combined repletion, and it also exacerbates the cognitive deficits associated with the combined deficiency (Baumgartner et al. 2012b). As mentioned earlier, iron is a co-factor of the enzymes responsible for the conversion of ALA to EPA and DHA. Thus, the provision of ALA with iron might be more effective in restoring brain EPA and DHA levels and improving cognition in double-deficient rats than ALA alone. Therefore, Baumgartner, Smuts, and Zimmermann (2014) supplemented adult male

Table 1. Key points of interaction between iron and omega-3 fatty acids metabolisms.

Key points	Reference
Liver is an organ of a great importance for iron-omega-3 fatty acids interactions. Iron supplemented rats show decreased activity of hepatic delta-5 and delta-6 desaturases with simultaneous decrease of hepatic levels of omega-3.	Valenzuela et al. (2018); Barrera et al. (2020)
Sterol regulatory element-binding protein (SREBP) seems to be positively regulated by iron and negatively by omega-3 fatty acids.	Valenzuela et al. (2018); Barrera et al. (2020); Masterton, Plevris, and Hayes (2010)
Iron and omega-3 fatty acids affect cholesterol levels. In mice, iron overload was correlated with elevated hepatic cholesterol, while iron deficiency decreases serum cholesterol concentrations in humans and rats. In turn, omega-3 fatty acids decrease the level of plasma cholesterol in obese individuals.	Graham et al. (2010); Prasnicka et al. (2017); Kasbi Chadli et al. (2013); Berard, Dumon, and Darmon (2004); Kasbi Chadli et al. (2013); Pizzini et al. (2017)
Metabolisms of both iron and omega-3 fatty acids are disturbed in nonalcoholic fatty liver disease (NAFLD). The meaningful role in disease progression has ability of both dietary components to modulate activity of enzyme crucial for pathogenic accumulation of lipids, including SREBP, stearoyl-CoA desaturase (SCD), and proliferator-activated receptor alpha (PPARα). Another major factor related to NAFLD is oxidative stress. High hepatic iron levels favor oxidative stress, while omega-3 fatty acids contradict this effect.	McNamara et al. (2012); Wu, Baylin, and Colacino (2018); Pigeon et al. (2001); Nelson, Klintworth, and Kowdley (2012); Minamiyama et al. (2010); MacDonald et al. (2001); Fujita et al. (2009); Videla et al. (2004); Zuniga et al. (2011)
Iron and omega-3 fatty acids interact with each other in process called ferroptosis, which is characterized by ROS accumulation due to increased labile iron pool (LIP) levels and in turn due to massive lipid peroxidation, which may perturb cellular membrane transport or mitochondrial function. Ferroptosis has been implicated in the pathological cell death associated with degenerative diseases, carcinogenesis, stroke, traumatic brain injury, and others.	Stockwell et al. (2017); Weiland et al. (2019); Dixon et al. (2012); Magtanong and Dixon (2018); Xie et al. (2016)
Studies on African children have shown that the combination of iron supplementation with omega-3 fatty acids prevented increase in respiratory morbidity, comparing to supplementation with iron alone. This effect may be caused by omega-3 supplementation, which alter the profile of the lipid-derived immune modulators to being more anti-inflammatory or pro-resolving.	Malan et al. (2015); Malan et al. (2016)
Iron metabolism links with omega-3 fatty acid levels in the context of cognition in rats and humans. In young rats exist additive and interactive effects of concurrent iron deficiency and essential ALA fatty acids on brain monoamine concentrations and spatial working and reference memory. In turn in children with iron deficiency anemia and poor omega-3 fatty acid status iron supplementation has beneficial effects on cognition.	Baumgartner et al. (2012a, 2012b, 2012c); Baumgartner, Smuts, and Zimmermann (2014)

iron- and omega-3 DHA/EPA-deficient rats with ALA and iron, alone and in combination, and analyzed brain monoamine concentrations and cognitive performance. This experimental model reflects children from underdeveloped countries born to mothers with poor fatty acid status, who have a low-iron diet throughout childhood and then start to consume sufficient levels of both nutrients only in early adulthood. The provision of ALA in combination with iron to double-deficient rats enhanced the conversion of ALA into its respective long-chain derivative DHA in the brain. They demonstrated that rats replete with ALA or iron alone showed no learning effect in the reference memory task. Rats that had received ALA in combination with iron exhibited a marked improvement. These data, in contrast to a previous study, showed that the provision of ALA had a beneficial effect on reference memory, particularly when provided in combination with iron, which may be explained by the enhancing effect of iron on the conversion of ALA to DHA in the hippocampus (Baumgartner, Smuts, and Zimmermann 2014). This study was consistent with a recent report showing that iron-deficient rats subjected to a diet enriched with iron and a mixture of essential fatty acids, containing equal amounts of LA and ALA, exhibited improved learning and memory performance in the Morris Water Maze compared with controls, while the rats fed with iron alone performed worse (Yehuda et al. 2008).

Similar research by Baumgartner, Smuts, Malan, Kvalsvig, et al. (2012) assessed the cognitive functions in 6- to 11-year-old iron-deficient children who received iron and omega-3 DHA/EPA supplementation alone and in combination. A group of children with mild iron deficiency anemia receiving iron and PUFA supplementation had higher weight-for-age *z* scores at the endpoint. In contrast to a previous animal study, the authors showed that iron supplementation has beneficial effects on cognition in children with iron deficiency anemia and poor omega-3 fatty acid status. Unexpectedly, however, DHA/EPA supplementation had no benefit on cognition in children with poor omega-3 fatty acid status and iron deficiency. Additionally, DHA/EPA supplementation had a strong negative effect on the working memory in children with iron deficiency anemia and on long-term memory and retrieval in girls with iron deficiency, whereas boys with iron deficiency tended to benefit from the DHA/EPA supplementation (Baumgartner, Smuts, Malan, Kvalsvig, et al. 2012).

As mentioned above, both iron deficiency and poor omega-3 fatty acid status have been associated with behavioral changes in children (Harahap et al. 2000; Kennedy et al. 2009). There are a limited number of studies concerning the interplay between iron and omega-3 fatty acids in terms of physical activity. A study by Smuts et al. (2015) provided evidence that DHA/EPA supplementation for healthy South African children might decrease physical activity levels during class time and that lower activity levels at the endpoint were associated with lower levels of teacher-rated hyperactivity.

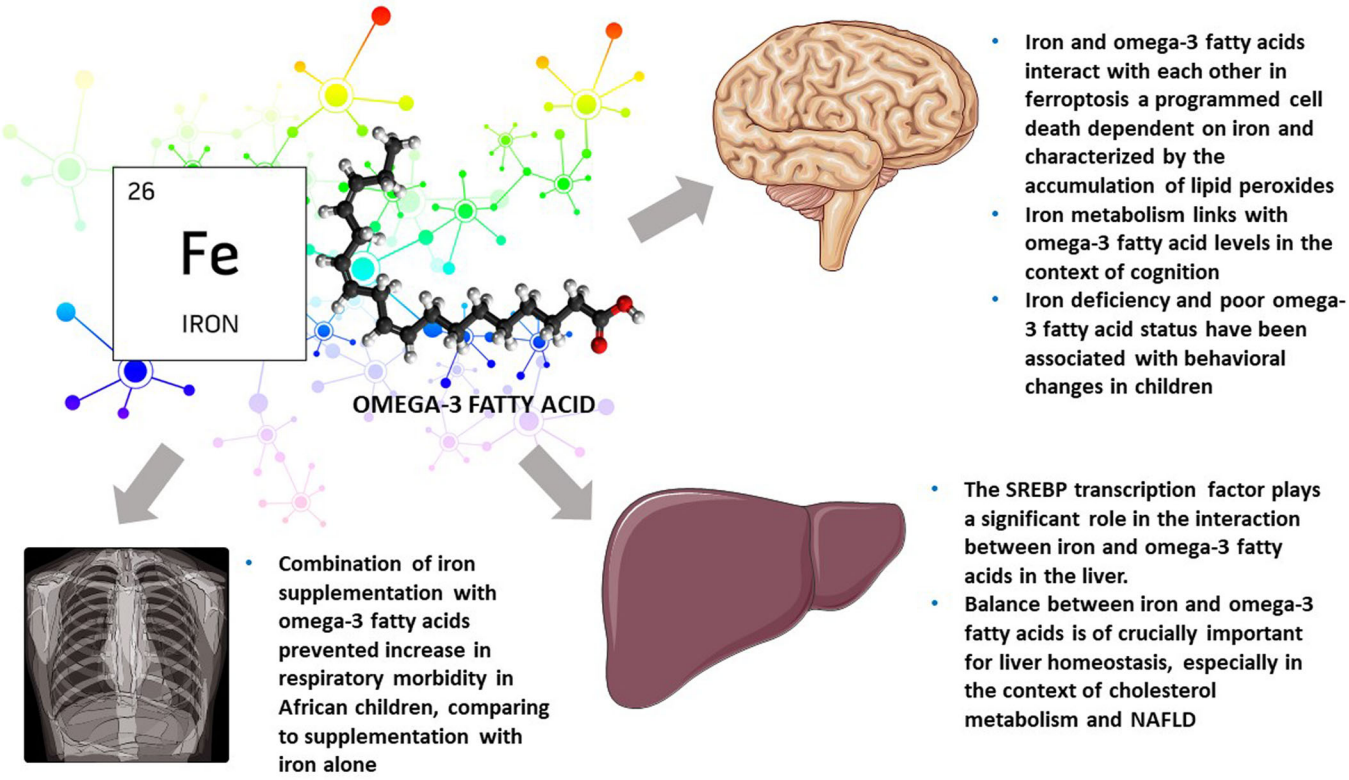

Figure 3. The illustration of the key interactions between iron and omega-3 fatty acids metabolisms.

Opposite behavior has been noticed in iron-deficient, DHA/EPA-supplemented healthy South African children (Smuts et al. 2015), while a three-month school meal intervention based on a Nordic diet of increased dietary iron content and fish (Andersen et al. 2014) improved reading performance and increased the percentage of errors in the d2-test of attention, i.e., it increased inattention and impulsivity, in 8- to 11-year-old Danish children (Sorensen et al. 2015). This research has been extended by the analysis of "school performance" and inattention in correlation to serum omega-3 fatty acid concentration. The dose–response relationship suggested that approximately 20% of the intervention effect on "school performance" could be related to the increase in omega-3 fatty acid status. In agreement with this finding, omega-3 fatty acid status was positively associated with the previously reported intervention effects (Andersen et al. 2014) on reading performance. Furthermore, the results suggested that about 20% of the intervention effect on inattention (increased d2-error%) could be related to the omega-3 fatty acid status (Sorensen et al. 2015).

Conclusion

The growing number of studies in recent years clearly indicates the occurrence of cross-talk between iron metabolism and PUFA metabolism (Table 1, Figure 3), especially in the liver and brain. The liver is an organ of pivotal importance for both iron and omega-3 fatty acid metabolisms. The SREBP transcription factor plays a significant role in the interaction between iron and omega-3 fatty acids in the liver. The clear evidence for a cross-link between these two dietary components implies a need for new approaches to studies – studies aimed at analyzing their combined action to reveal the proper balance between iron and omega-3 fatty acids, which is crucially important for liver homeostasis, especially in the context of NAFLD.

Although iron dysregulation has been implicated in several neurodegenerative diseases, the mechanisms involved in these processes are still poorly understood. Further research, focused especially on the role of ferroptosis and on the participation of omega-3 fatty acids in this process, would provide a better understanding of the etiology of these disorders. In vitro and in vivo studies using ferroptosis inhibitors offer great hope for treating and slowing down the progression of neurological diseases. Therefore, in the context of our knowledge about the influence of diet composition on learning performance, cognition, and behavior in early childhood, it is worth quoting the old maxim of Jean Anthelme Brillat-Savarin: "Tell me what you eat, and I will tell you what you are."

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