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Oxidative Metabolism of Iron: Can Something Good for Health be Harmful When it is Supplemented In Excess?

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ABSTRACT

The purpose of this commentary is to briefly summarize the central role of Fe in terms of oxidative effects on health, indicating the impact of Fe overload due to either exogenous supplementation or to the generation of cellular Fe excess content due to pathological situations. Fe is an element responsible for different effects depending on whether its action is as micronutrient or as a catalyst for the generation of free radicals. Thus, Fe metabolism is very complex and many advances are still required in order to know in detail the nature and function of catalytically active Fe in cells. Therefore, alterations in Fe oxidative metabolism must be carefully analyzed before taken intervention actions for either, therapeutic purposes or in actions linked to public health policies (food supplementation with Fe) to avoid Fe-dependent deleterious effects.

FEATURES OF IRON (FE) METABOLISM

Fe is an essential micronutrient for organisms and plays a central role in essential cellular functions, such as Oxygen (O_2) transport, energy metabolism of mitochondria and electron transport since it is part of oxidases and oxygenases. Fe is present in the diet in both, heme and non-heme compounds, but its bioavailability is low [1]. Its absorption depends on a large number of factors related to the nature of the food and to the organism being feed with it. Complexing agents naturally present in foods, such as sugars, amino acids, ascorbic acid, and glycoproteins, can form complexes with Fe by maintaining it in a soluble form and favoring its absorption, while phytates, phosphates and carbonates, oxalates, bicarbonates, and dietary fiber bind Fe forming relatively insoluble complexes [2]. Normal adult individuals have an Fe content in the body of 3-4 g and the concentration is mainly regulated by ingestion. Fe, that is transported in the blood bound to specific proteins such as Transferrin (Tf) and lactoferrin, is taken by cells by forming the Tf-Fe^{3+} complex in the cell surface Tf receptor, with the subsequent reduction of the Fe^{3+} to Fe^{2+} and release from the endosome to the cytosol. The system hepcidin-ferroportin was discovered at the beginning of the 21th century. Hepcidine is a 25 aminoacids polypeptide hormone synthesized in liver cells whose target is the Ferroportin (FPN) receptor. FPN is a transmembrane protein, which is the only Fe exporting transporter in Fe mobilizing cells. In these cells the Fe extruded is proportional to the expression of FPN on their surface membrane. When hepatocyte produced serum hepcidine, reaches its target, the hepcidine-FPN complex is interiorized and degraded in the cell lysosomal system,

reducing FPN and the cell capacity of exporting Fe. As a result, Fe absorption as well as Fe recycling and serum Fe are reduced [3]. There is Fe stored in Ferritin (Ft) and hemosiderin in mammalian cells [1]. Fe is absorbed into intestine via metal transporter 1 (DMT1). The Fe can be released from intestine and get into blood stream via the FPN. In blood stream, the Fe binds with Transferrin (Tf) and can get into cells via Tf receptor. In cells, Fe can bind with Ft HL and L chains as storage pool or Fe can get into mitochondria via ABCB10 transporter. In mitochondria, Fe can bind with mitoferritin (FTMT). Furthermore the Ft and Tf expression is controlled by the Iron Regulatory Protein (IRP) signaling pathway [4]. Circulating Ft has also been found in human plasma. In addition, a pool of Fe in transit known as Labile Fe Pool (LIP), has been described within the cell. The LIP is defined as the Fe found in the cytosol bound to low molecular weight compounds, and the exact nature of this pool is unknown, but it is proposed to include substances such as ATP, GTP, ADP, citrate, oxalate, etc. [5]. Thus, the total Fe in an organism is distributed in functional compounds, storage complexes and transport chelates in mainly the liver, spleen, and marrow. No Fe excretion mechanisms have been described, but it seems to be simply eliminated through the replacement of epithelial cells of the intestine, skin, sweat, feces (partially from the bile), and urine [5].

DEREGULATION OF FE METABOLISM AND HUMAN DISEASES

Alterations in Fe metabolism cause Fe deficiencies due to bleeding losses, and nutritional problems. Approximately 30% of the world's population faces problems of Fe deficiency, and treatment with Fe supplements has been known for centuries. However, at present, interest has been focused on designing treatments to improve the availability of Fe in non-heme foods to favor human food nutritional quality. Fe overload occurs due to excessive intestinal absorption, parenteral administration, inhalation, mobilization from organs to plasma, diseases linked to Fe accumulation, etc. Fe overload has been associated with cellular injury, fibrosis and cirrhosis of the liver in mammals, heart disease, endocrine abnormalities, osteoporosis and skin pigmentation [6]. The diagram presented in (Figure 1) summarized several pathological conditions currently associated with Fe overload. Fe in excess enhances microbial infection, interferes with chemotaxis, phagocytosis, and the microbicidal action of leukocytes, also reduces the migration of B and T lymphocytes into the lymphatic system, the number of interleukine-2 (IL-2) secreting cells and of T-helper cells, the activity of natural killer cells and the tumoricidal action of macrophages [7]. It may also be associated with more advanced hepatic fibrosis in patients with chronic hepatitis C virus infection [8]. The sites of the tumors tend to be associated with the sites of the deposit of Fe, e.g. sarcomas at sites of intramuscular injection of Fe, primary hepatocellular carcinoma in hemocromatotic, siderotic, and/or alcoholic patients, respiratory tract neoplasia and colorectal cancer [7,9,10]. It was also reported that myocardial cells have a greater affinity for Fe than skeletal or smooth muscle cells. In adults chronically stressed with excess Fe, the most common cause of death is heart failure. Women enjoy certain degree of protection from ischemic heart disease before menopause (Weinberg, 1990). Fe ions have a role in atherosclerosis pathology [11]. The elevated level of 8-hydroxy-2'-deoxyguanosine in lymphocytes of atherosclerotic patients showed a good correlation with the LIP [12]. Dysfunction of endothelial cells may contribute to cardiovascular diseases [13]. It was also suggested an important pathogenetic role of accumulation of Fe in the deposits in patients with chronic liver diseases (cirrhosis, hepatomegaly, hepatocellular carcinoma) [14,15], obesity, type II diabetes [16] and hypertension [17]. Fe overload induced diseases also include gene mutation induced human diseases and human disorders with Fe overload. The HFE gene mutation can induce Haemochromatosis with Fe overload. The mutations in the Ft-L Fe-Responsive Element (IRE) can impair IRP binding, leading to hereditary hyperferritinaemia cataract syndrome. The neuroferritinopathy can be associated with L-Ft mutation. Furthermore, Fe overload is related to human neuron degenerative diseases, including Parkinson's Disease (PD), Alzheimer's Disease (AD) and multiple system atrophy (MSA), etc. [6]. There is Fe accumulation in affected brain areas [18]. Moreover, in the toxic mechanism related to Fe relationship with PD, the Fe species were identified to induce dopamine oxidation and subsequent dopamine quinone and ROS toxicity [19].

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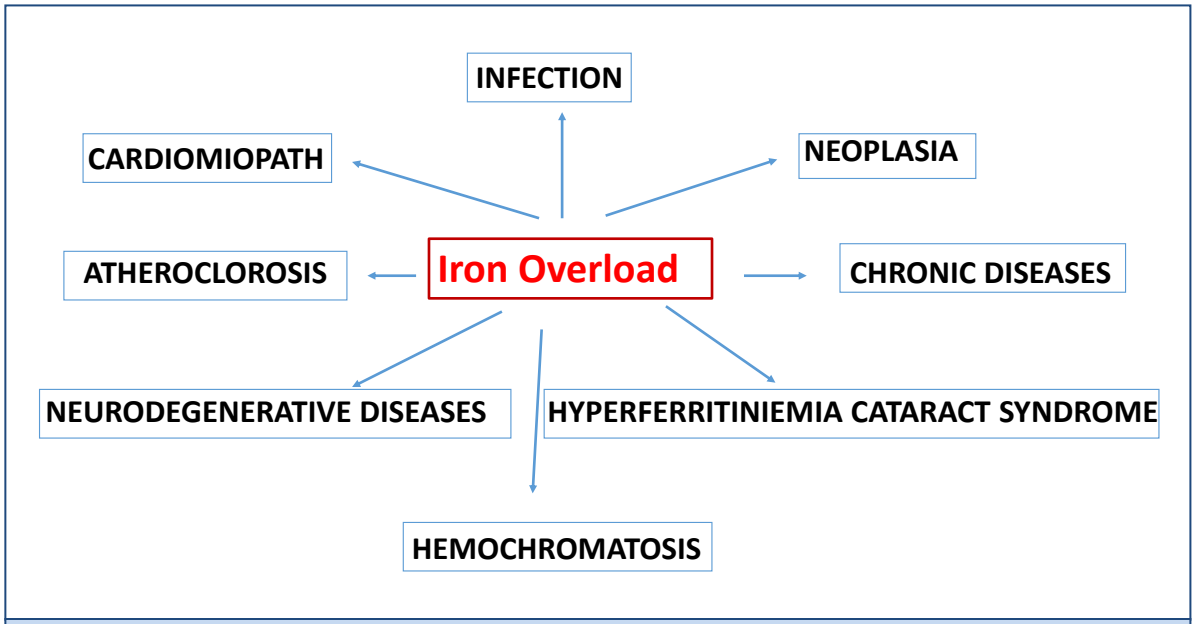

Figure 1: Main groups of diseases that occur linked to cellular Fe overload.

TOXIC MECHANISMS OF FE SPECIES. FE AND OXIDATIVE STRESS

Fe not strongly bound to proteins is considered the main catalyst for the formation of reactive species of O_2 (ROS) and N2 (RNS) that could be a factor to damaging membranes (lipids and proteins) and DNA. Thus, it is critical for cells to maintain Fe homeostasis to be able to ensure its supplementation but preventing the excess [20]. Fe contains missing electrons and can be considered as a radical. Fe is a suitable catalyst for the generation of highly reactive intermediates that would be responsible for generating oxidative stress, understood as an increase in the steady state concentration of ROS and RNS reactive species in the cells. The LIP catalyzed the conversion of normal by-products of cell respiration, like superoxide anion (O_2-) and hydrogen peroxide (H_2O_2), into highly damaging hydroxyl radical (•OH) through the Fenton reaction (reaction 1) or by the Fe^{2+} catalyzed Haber-Weiss reaction (reaction 2), or into equally aggressive ferryl ions or O_2-bridged Fe^{2+}/Fe^{3+} complexes. Fe^{3+} can be reduced either by O_2- (reaction 3) or by ascorbate (AH-) leading to ascorbyl radical ($A^{\bullet}$) production (reaction 4).

$$Fe^{2+} + H_2O_2 \Rightarrow Fe^{3+} + HO^- + {}^{\bullet}OH \quad (1)$$

Fe

$$O_2^- + H_2O_2 \Rightarrow O_2 + HO^- + {}^{\bullet}OH \quad (2)$$

$$Fe^{3+} + O_2^- \Rightarrow Fe^{2+} + O_2 \quad (3)$$

$$Fe^{3+} + AH^- \Rightarrow Fe^{2+} + A^{\bullet}$$

However, depending on the magnitude of the oxidative stress, the span of the exposure to that condition, and the endogenous antioxidant abilities of the organisms the effects of these reactive species can vary. The diagram shown in (Figure 2), indicates that facing Fe overload the cell could respond to the increasing Fe catalytic actions in a different ways. Damage induced by lipid peroxidation is the unifying mechanism in all theories of cellular injury due to severe Fe overload. The effects of Fe overload on the liver had been extensively studied, also focusing on the source of Fe. The acute administration of Fe-dextran leads to the deposit of the Fe in the Endotelial Reticulum System [21], meanwhile the administration of Fe in a chronic form with carbonyl-Fe favors the deposition in hepatocytes [22]. However, in the brain and, mainly due to the presence of the blood brain barrier, it has been considered that the Fe-dependent oxidative effects would not be as dramatic as those described in the liver and, thus it have received less attention. Recent studies indicate that

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Fe overload, both acute [18,23] and subchronic [24,25] lead to a significant increase in Fe brain content and the establishment of conditions of alterations in cellular oxidative balance has been demonstrated. However, if ROS are produced in moderate concentrations, they can act as second messengers in signal transduction and gene regulation in a variety of cell types and biological conditions [26]. Recently, the concept of hormesis has been enunciated. Hormesis is a dose-dependent response that is interpreted as a phenomenon with beneficial effects at low concentrations and harmful responses at high levels of concentration and/or after prolonged exposure to ROS [27]. Videla [28] reported that cells and organisms exposed to moderate conditions of oxidative stress respond by inducing protective mechanisms. The response is induced by low doses of toxic agents, radiation, ROS, dietary caloric restriction, moderate exercise and heat stress [28]. Currently, the ability of different Fe administration protocols is being studied, for the possible induction of mechanisms that partially or totally prevent the toxicity of stress situations such as liver ischemia-reperfusion [29], or treatment with therapeutic drugs in the brain (for example, chlorpromazine, CPZ). Piloni et al. [30] tested the hypothesis stating that administration of Fe leads to a specific response by the antioxidant network in the rat brain, that could modulate the effect of later oxidative challenges (such as, CPZ administration) on the cells. The effect of both, acute and subchronic Fe overload treatment on rat brain DNA integrity, and lipid radical (LR●) generation rate was studied and, the effect of CPZ supplementation after Fe overload on brain antioxidant capacity was characterized. From this study, it was proposed that Fe triggers a hormetic protective response that limits oxidative damage to the brain, depending on the pattern of Fe administration (acute or subchronic). Much progress still needs to be made in order to understand the nature and function of Fe and, mostly of the LIP, as contributors to oxidative stress and disease, as well as the role of Fe-dependent stress in the development of possible chemotherapeutic strategies.

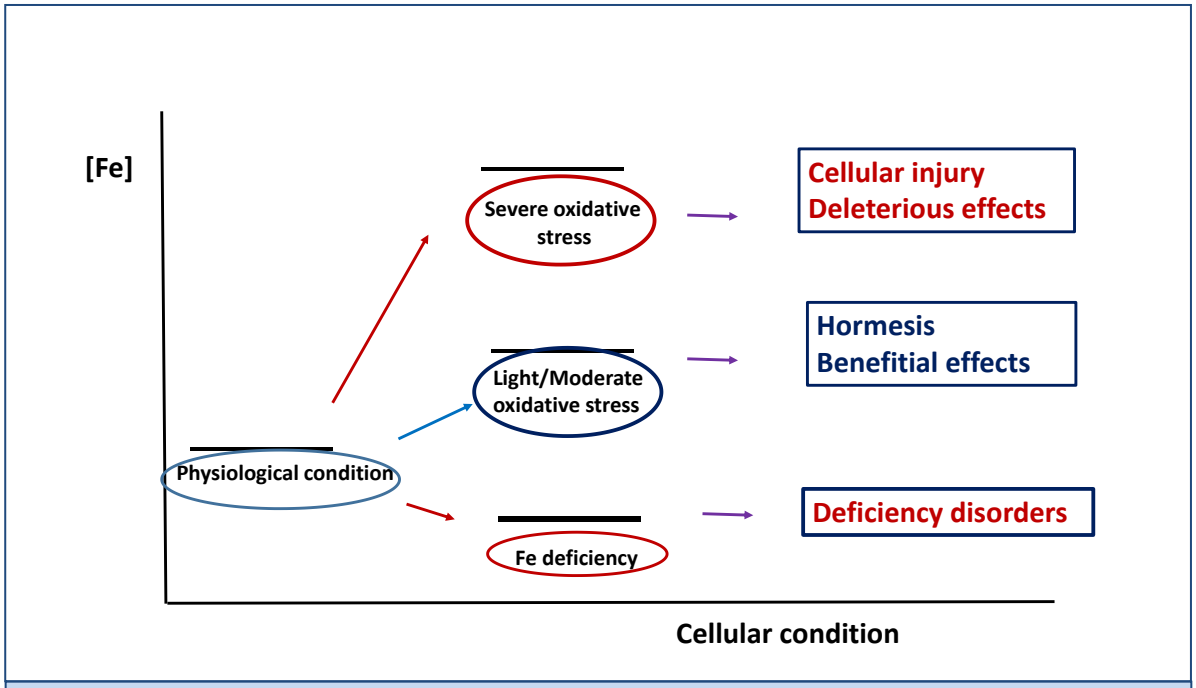

Figure 2: Schematic picture describing the changes is Fe steady state concentration and their effects on the cellular status.

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THERAPIES AGAINST FE RELATED TOXICITY

Important advances have been made in the knowledge of conditions that involves localized Fe-overload. Those conditions would include short term processes, as organ or tissue ischemia-reperfusion and local inflammation, as well as progressive pathologies essentially affecting the central nervous system. In the first case, the decompartamentalization of Fe would lead to the expansion of the LIP and the increase of the oxidative damage, being a potential situation where Fe chelators would protect the tissues [6]. In the second case, it has been described an increase in Fe levels in the substantia nigra of Parkinsonian brains [31], Hallervorden-Spatz syndrome [32] and in mitochondria of Friedrich´s ataxia cerebella [33]. Chelation therapy of Fe from those particular compartments constitutes a wide field under active research. In designing Fe chelators for clinical application two different aspects should be considered: i) chelating chemical aspects, including metal selectivity, complex stability and redox activity, and ii) pharmacological aspects, such as administration routes, ability of the compound to reach the target site and toxicity [6]. An important number of chemical families have been studied in order to find molecules able to fulfil the requirements for optimal performance as Fe chelators in vivo: hydroxamic acids, aminocarboxylates, catechols, hydroxypyridones, pyridoxal isonicotinoyl hydrazone, desferrithiocins, triazoles, dialkylhydroxypyridinones, and hydroxypyridinone derivatives, extensively reviewed by Hershko and Weatherall [34], Liu and Hider [35], and by Crisponi and Remelli [36]. Despite the efforts, DFO (Desferal®), deferiprone (DFP) or L1 (Ferriprox®) and deferasirox (DFS) or ICL670 (Exjade®) are the only products currently used in therapeutics [37]. The effect of Fe chelators on the oxidative stress parameters of Fe overloaded patients has been widely documented. Moreover, the DFO and DFS were comparatively studied in beta-thalassemic patients and oxidative stress was evaluated [38].

The main features of the optimal Fe chelator include chemical, as well as pharmacological aspects. Chemical aspects to be considered include Fe-affinity, Fe-selectivity, molecular weight, and lipophilicity, in addition to stability and redox properties of the resultant Fe-complex. Among the pharmacological issues, administration routes, ability of the compound to reach the target site and toxicity are required to be taken into account.

Currently clinical research is focused on the challenge of designing a Fe chelator with the efficiency of DFO but that could be administered orally to meet critical goals such as good performance and comfort for the patient (Puntarulo and Galleano, 2009). The understanding of the chemical-related aspects of the Fe-chelator complexes should help to fulfil the new drugs designing expectances.

CONCLUSIONS AND REMARKS

The integrated analysis of this information highlights the need for a very prudent approach to intervention actions for either, therapeutic purposes or in situations such as those required by health policies (e.g. food supplementation with Fe), to avoid damage to health. In this sense, it is critical to mention the importance of having a greater flow of basic biochemical knowledge to achieve successfully the goal of improving the protection of the health of the individual, and the optimization and effectiveness of medical procedures. Thus, it is critical to consider the complex metabolism of Fe, which is essential for numerous cellular processes, but in excess could lead to cellular damage by oxidative reactions. Therefore, it requires the careful designing of strategies to maintain its level within a very tight range of steady state concentrations that allows its availability for those reactions in which it is a fundamental component, but minimize its participation as a catalyst in the production of toxic species. Also, based on the recent results that indicate that even an excess of Fe can be beneficial, it seems clear the requirement of having clear mechanistic information on Fe-dependent pathways that would allow the designing of the administration protocols that could be useful in therapeutic treatments.

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