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Review Article

The complex interplay of iron metabolism, reactive oxygen species, and reactive nitrogen species: Insights into the potential of various iron therapies to induce oxidative and nitrosative stress

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ABSTRACT

Production of minute concentrations of superoxide ($O_2^{\bullet -}$) and nitrogen monoxide (nitric oxide, $NO^{\bullet}$) plays important roles in several aspects of cellular signaling and metabolic regulation. However, in an inflammatory environment, the concentrations of these radicals can drastically increase and the antioxidant defenses may become overwhelmed. Thus, biological damage may occur owing to redox imbalance—a condition called oxidative and/or nitrosative stress. A complex interplay exists between iron metabolism, $O_2^{\bullet -}$, hydrogen peroxide (H_2O_2), and $NO^{\bullet}$. Iron is involved in both the formation and the scavenging of these species. Iron deficiency (anemia) (ID(A)) is associated with oxidative stress, but its role in the induction of nitrosative stress is largely unclear. Moreover, oral as well as intravenous (iv) iron preparations used for the treatment of ID(A) may also induce oxidative and/or nitrosative stress. Oral administration of ferrous salts may lead to high transferrin saturation levels and, thus, formation of non-transferrin-bound iron, a potentially toxic form of iron with a propensity to induce oxidative stress. One of the factors that determine the likelihood of oxidative and nitrosative stress induced upon administration of an iv iron complex is the amount of labile (or weakly bound) iron present in the complex. Stable dextran-based iron complexes used for iv therapy, although they contain only negligible amounts of labile iron, can induce oxidative and/or nitrosative stress through so far unknown mechanisms. In this review, after summarizing the main features of iron metabolism and its complex interplay with $O_2^{\bullet -}$, H_2O_2, $NO^{\bullet}$, and other more reactive compounds derived from these species, the potential of various iron therapies to induce oxidative and nitrosative stress is discussed and possible underlying mechanisms are proposed. Understanding the mechanisms by which various iron formulations may induce oxidative and nitrosative stress will help us develop better tolerated and more efficient therapies for various dysfunctions of iron metabolism.

Abbreviations: ACD, anemia of chronic disease; AID, absolute iron deficiency; ARE, antioxidant-responsive elements; asc, ascorbic acid; DMT1, divalent metal transporter 1; eNOS, endothelial nitric oxide synthase; EPO, erythropoietin; FBXL5, F-box and leucine-rich repeat protein 5; FCM, ferric carboxymaltose; Fe-EDTA, sodium Fe(III) ethylenediaminetetraacetic acid; FG, ferric gluconate; FID, functional iron deficiency; FMX, ferumoxytol; FPN, ferroportin; GI, gastrointestinal; GPx, glutathione peroxidase; GSH, glutathione; Hb, hemoglobin; HIF, hypoxia-inducible factor; HO-1, heme oxygenase 1; ID(A), iron deficiency (anemia); IIM, iron isomaltoside 1000; IL, interleukin; iNOS, inducible nitric oxide synthase; IPC, iron polymaltose complex; IPCS, iron polymaltose complex similar; IRE, iron-regulatory element; IRP, iron-regulatory protein; IS, iron sucrose; ISS, iron sucrose similar; iv, intravenous; LIP, labile iron pool; LMWID, low-molecular-weight iron dextran; MDA, malondialdehyde, MPS, mononuclear phagocyte system, NF-κB, nuclear factor-κB; nNOS, neuronal nitric oxide synthase; Nramp1, natural resistance-associated macrophage protein 1; Nrf2, NF-E2-related factor 2; NTBI, non-transferrin-bound iron; PHD, prolyl hydroxylase; PSC, polyglucose sorbitol carboxymethyl ether; RNS, reactive nitrogen species; ROS, reactive oxygen species; SOD, superoxide dismutase; Steap3, six-transmembrane epithelial antigen of the prostate 3; TfR, transferrin receptor; TNF-α, tumor necrosis factor α; TRPML1, transient receptor potential cation channel, mucolipin subfamily, member 1; TSAT, transferrin saturation; UTR, untranslated region; VHL, von Hippel–Lindau

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Contents

Introduction

Physiologically relevant reactive oxygen species (ROS)[1] and reactive nitrogen species (RNS) include superoxide ($O_2^{\bullet -}$), nitrogen monoxide (nitric oxide, $NO^{\bullet}$), hydroxyl radical ($HO^{\bullet}$), trioxidocarbonate ($^{\bullet}1^{-}$) ($CO_3^{\bullet -}$), nitrogen dioxide ($NO_2^{\bullet}$), hydrogen peroxide (H_2O_2), peroxynitrite ($ONOO^-$), and oxidochlorate (1^-) (OCl^-, hypochlorite) [2]. The concentrations of these species are kept within a narrow range by balancing the rate of production with the rate of removal by enzymatic antioxidants, such as superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase, or nonenzymatic antioxidants, such as ascorbic acid (asc; vitamin C), α-tocopherol (vitamin E), glutathione (GSH), urate, carotenoids, cysteine, bilirubin, and flavonoids.

$O_2^{\bullet -}$ and $NO^{\bullet}$ are produced by enzymes at low concentration during normal cellular metabolism (Fig. 1) and, together with H_2O_2, which is produced by dismutation of $O_2^{\bullet -}$, these species play an important role in cellular signaling and regulation [3]. Interestingly, it has been proposed that $O_2^{\bullet -}$ and H_2O_2 produced within cells and, in particular, within mitochondria can stimulate beneficial responses to the cellular stresses induced by aging, such as mitochondrial dysfunction and DNA damage [4]. Among others, $O_2^{\bullet -}$ and H_2O_2 have been shown to induce autophagy as well as DNA base excision repair systems [5]. However, under inflammatory conditions an oxidative burst from activated neutrophils and macrophages may lead to drastically elevated concentrations of $NO^{\bullet}$ and $O_2^{\bullet -}$ [6,7] resulting in the formation of other more reactive oxidants such as $ONOO^-$. Under these conditions, antioxidant defenses may become overwhelmed and biological damage of lipids, proteins, and DNA may occur, a condition termed oxidative or nitrosative stress. Oxidative and/or nitrosative stress can cause disruptions in normal cellular signaling mechanisms thereby severely compromising cell viability [8].

The production of $O_2^{\bullet -}$ and $NO^{\bullet}$ can exceed the capacity of detoxifying systems, resulting in oxidative stress [3] even under normal conditions. In humans, oxidative and/or nitrosative stress has been shown to be involved in many diseases and medical conditions, such as cancer, diabetes, Parkinson disease, Alzheimer disease, atherosclerosis, congestive heart failure, myocardial infarction, or schizophrenia [3,8]. Interestingly, biological aging also correlates with the accumulation of oxidized biomolecules in many tissues [3,8].

Most of the iron in the body is bound in hemoglobin and myoglobin, in which the metal is responsible for the reversible binding and release of oxygen. One of the most important properties of iron, both for its essential role and for its toxicity in living organisms, is the ability to redox cycle under physiological conditions. Iron is also the essential component in a large number of enzymes, which take advantage of its redox-cycling property to carry out electron transfer, to activate dioxygen to hydroxylate and to oxidize substrates, and to catalyze a variety of reactions, such as DNA [9], $NO^{\bullet}$, and thyroid hormone (T3, T4) synthesis [10]. Moreover, iron has been linked to the regulation of effective immune responses against infection with various pathogens [11]. However, because of its ability to redox cycle, iron may also promote formation of $HO^{\bullet}$ or a reactive higher oxidation state of iron (see Iron-induced generation of hydroxyl radicals), e.g., via the Fenton reaction [2]. Therefore, to avoid metal-induced toxicity iron must always be bound in a non-redox-active form, e.g., as found in transferrin and ferritin [9,12].

The interplay of iron with H_2O_2 and $O_2^{\bullet -}$ is complex, because these species play important roles in regulating iron metabolism [13,14]. Similarly, a complex interaction exists between iron metabolism, $NO^{\bullet}$, and, to a minor extent, $ONOO^-$ [15,16]. $NO^{\bullet}$ has a high affinity for Fe(II) and thus reacts with iron-containing proteins, affecting their activity [17]. $NO^{\bullet}$, $ONOO^-$, and possibly $NO_2^{\bullet}$, are also directly involved in the regulation of cellular iron homeostasis by modulating the binding affinity of iron-regulatory proteins (IRPs) to iron-responsive elements (IREs) [18–23]. In addition, cellular iron content influences macrophage activation and effector functions by inhibiting the activity of stimulatory

[1] Ferrous sulfate and ferrous fumarate are used throughout this paper as these are the common names of the two oral iron drugs. However, the terms "ferrous" and "ferric" to indicate Fe(II) and Fe(III), respectively, are outdated and do not conform to the current IUPAC recommendations [1].

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