Free Radical Biology and Medicine 72 (2014) 23–40

Contents lists available at ScienceDirect

Free Radical Biology and Medicine

journal homepage: www.elsevier.com/locate/freeradbiomed

Review Article

Physiology and pathophysiology of iron in hemoglobin-associated diseases

Thomas D. Coates

Children's Center for Cancer and Blood Diseases, Children's Hospital Los Angeles, University of Southern California Keck School of Medicine, Los Angeles, CA 90027, USA

ARTICLE INFO

Article history:
Received 14 February 2014
Received in revised form
26 March 2014
Accepted 27 March 2014
Available online 12 April 2014

Keywords:
Hemoglobinopathy
Thalassemia
Iron overload
Hemochromatosis
Sickle cell disease
Magnetic resonance imaging
Chelation
ROS
Iron toxicity
Transfusion

ABSTRACT

Iron overload and iron toxicity, whether because of increased absorption or iron loading from repeated transfusions, can be major causes of morbidity and mortality in a number of chronic anemias. Significant advances have been made in our understanding of iron homeostasis over the past decade. At the same time, advances in magnetic resonance imaging have allowed clinicians to monitor and quantify iron concentrations noninvasively in specific organs. Furthermore, effective iron chelators are now available, including preparations that can be taken orally. This has resulted in substantial improvement in mortality and morbidity for patients with severe chronic iron overload. This paper reviews the key points of iron homeostasis and attempts to place clinical observations in patients with transfusional iron overload in context with the current understanding of iron homeostasis in humans.

Contents

Abbreviations: BMP-6, bone morphogenetic protein-6; DMT1, divalent metal transporter-1; CDA, congenital dyserythropoietic anemia; CSA, congenital sideroblastic anemia; EPO, erythropoietin; FPN, ferroportin; GDF-15, growth differentiation factor-15; HbS, hemoglobin S; HFE, human hematochromatosis protein; HJV, hemojuvelin; IRP, iron-regulatory protein; IRE, iron-responsive element; LPI, labile plasma iron; LCI, labile cellular iron; LIC, liver iron concentration; MRI, magnetic resonance imaging; NTBI, non-transferrin-bound iron; RBC, red blood cell; ROS, reactive oxygen species; SCD, sickle cell disease; TBI, transferrin-bound iron; Tf, transferrin; TfR, transferrin receptor; ZIP14, ZRT/IRT-like protein 14

E-mail address: tcoates@chla.usc.edu

http://dx.doi.org/10.1016/j.freeradbiomed.2014.03.039
0891-5849/

Introduction

Toxicity and increased morbidity due to iron overload are common and well-recognized complications associated with various hemoglobin disorders. Chronic iron overload occurs primarily from repeated blood transfusions in a number of hematological disorders. In fact, the most extensive information regarding severe chronic iron overload comes from decades of experience with the management of patients with thalassemia major, a hemoglobinopathy in which the primary morbidity stems from iron overload and that is fatal, if untreated. The toxicity due to transfusional iron overload depends upon a number of factors in addition to the degree of tissue iron loading itself. Although our experience with thalassemia has been very helpful, it is not entirely applicable to all disorders associated with iron loading, as the patterns of tissue iron distribution and the severity of tissue damage differ among them.

Many advances in our understanding of the treatment of transfusional overload have occurred, particularly in the past 15 years. The ability to noninvasively measure tissue iron in humans by magnetic resonance imaging (MRI)[1], major breakthroughs in our understanding of the molecular physiology of iron regulation, and the availability of new iron-chelating agents have resulted in a dramatic improvement in the survival of patients with severe iron overload [1,2].

The purpose of this review is to summarize our current understanding of iron homeostasis, briefly introduce the hematological disorders primarily associated with iron overload, and discuss how new knowledge regarding iron homeostasis informs and is validated by observations made in the course of clinical monitoring and management of humans with transfusional iron overload.

Iron homeostasis

Biological organisms have evolved to conserve iron and as such, humans have no mechanisms for the excretion of iron. Approximately 1 to 2 mg per day, or about 0.05% of the total body iron, is lost through desquamation of the gastrointestinal tract lining and skin and, in small amounts, through blood loss [3]. This is balanced through absorption of dietary iron, primarily in the duodenum. Iron balance is maintained entirely through the regulation of absorption and recycling of iron from red cells. Iron absorption can be increased by as much as 20-fold in cases of acute blood loss (reviewed in [4,5]). Iron absorption can also be pathologically increased in certain genetic disorders of iron transport as well as in hemoglobin disorders associated with ineffective erythropoiesis. Fig. 1 summarizes key features of normal and pathologic iron balance.

Patients with hemoglobin disorders have significant differences in iron utilization, erythropoietic drive, and iron input from transfusion that result in pathological iron absorption, iron loading, and toxicity. In these patients, the relatively small changes in dietary absorption and minimal iron excretion are not sufficient to maintain iron balance.

Regulation of iron proteins

Iron balance is maintained by controlling the levels and function of iron transport proteins. Transferrin is the main plasma iron transporter that binds two molecules of ferric iron (Fe^{3+}). Transferrin is usually between 20 and 30% saturated with iron (see below). At the systemic level, transferrin saturation is the main iron sensor and plays a role in controlling the levels of the iron-regulatory peptide hepcidin. At the cellular level, there are two common mechanisms that apply to most of the proteins involved in iron homeostasis. First, iron-regulatory proteins 1 (IRP1) and 2 (IRP2) bind to iron-response elements (IREs) in the untranslated regions (UTRs) of mRNA encoding proteins involved in cellular iron uptake, storage, and export (transferrin receptor-1, TfR; divalent metal transporter-1, DMT1; ferritin-H/ferritin-L/ferroportin, FPN). IRP1/2 bind to IREs under conditions of low iron, and they dissociate from IREs in high-iron states (reviewed in [6]). If the IRE is in the 3′UTR, IRP binding stabilizes the mRNA, prevents degradation, and increases protein production. If the IRE is in the 5′UTR, mRNA translation is inhibited [6–8]. The second general mechanism imparts tissue-specific sensitivity to iron balance by modulation of the proportion of iron-sensitive and iron-insensitive mRNAs. At least for DMT1 and FPN, two different splice variants of mRNA exist, one with an IRE and the other without. This means that one variant responds to iron levels and one does not. The ratio of IRE to non-IRE differs in different tissues, resulting in differences in responsiveness to iron and differences in loading [9,10]. In general, the IRP/IRE system protects against iron loss. There are over 35 mRNAs, including hypoxia-inducible factor 2α, that have an IRE and are responsive to iron [7,11].