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Review

Current status of iron metabolism: Clinical and therapeutic implications☆

Susana Conde Diez[a], Ricardo de las Cuevas Allende[b], Eulogio Conde García[c,*]

[a] Medicina de Familia, Servicio Cántabro de Salud, Santander (Cantabria), Spain
[b] Medicina de Familia, Servicio Cántabro de Salud, Centro de Salud Bajo Asón, Ampuero (Cantabria), Spain
[c] Servicio de Hematología, Hospital Universitario Marqués de Valdecilla, Universidad de Cantabria, Santander (Cantabria), Spain

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ABSTRACT

Hepcidin is the main regulator of iron metabolism and a pathogenic factor in iron disorders. Hepcidin deficiency causes iron overload, whereas hepcidin excess causes or contributes to the development of iron-restricted anaemia in chronic inflammatory diseases. We know the mechanisms involved in the synthesis of hepcidin and, under physiological conditions, there is a balance between activating signals and inhibitory signals that regulate its synthesis. The former include those related to plasmatic iron level and also those related to chronic inflammatory diseases. The most important inhibitory signals are related to active erythropoiesis and to matriptase-2. Knowing how hepcidin is synthesized has helped design new pharmacological treatments whose main target is the hepcidin. In the near future, there will be effective treatments aimed at correcting the defect of many of these iron metabolism disorders.

Estado actual del metabolismo del hierro: implicaciones clínicas y terapéuticas

Palabras clave:
Metabolismo del hierro
Hepcidina
Ferroportina
Agonistas de la hepcidina
Antagonistas de la hepcidina

RESUMEN

La hepcidina es el principal regulador del metabolismo del hierro y el factor patogénico más importante en sus trastornos. La deficiencia de hepcidina provoca sobrecarga de hierro, mientras que su exceso da lugar o contribuye al desarrollo de anemias por déficit o restricción de hierro en las enfermedades crónicas. Conocemos los mecanismos implicados en la síntesis de hepcidina y, en condiciones fisiológicas, hay un equilibrio entre las señales activadoras e inhibidoras que regulan su síntesis. Las primeras incluyen las relacionadas con la concentración plasmática de hierro y con las enfermedades inflamatorias. Las señales inhibidoras más importantes están relacionadas con la eritropoyesis activa y con la matriptasa-2. Conocer cómo se sintetiza la hepcidina ha servido para diseñar nuevos tratamientos farmacológicos cuya diana principal es la hepcidina. En un futuro próximo, se dispondrá de tratamientos eficaces dirigidos a corregir el defecto de muchos de los trastornos del metabolismo del hierro.

Introduction

Iron is an essential nutrient in the body which plays a central role in cellular energy metabolism, anaerobic respiration, synthesis of haemoglobin and nucleotide synthesis, additionally, it is also involved in many other processes of exudative metabolism and cellular immune response.[1] In the adult, the total amount of iron in the body is 3–4 g, of which 65% is in haemoglobin, 25% in deposit organs (liver, reticuloendothelial system macrophages and bone marrow) and the remaining 10% in myoglobin, cytochromes, peroxidase and catalases.[2] Every day, 1–2 mg/d of iron is absorbed from the diet, which is the same amount lost daily, but it should be noted that the organism does not have an active iron excretion mechanism, so that control of the duodenal absorption plays a vital role in iron homeostasis.[3] Plasma iron circulates bound to transferrin and it comes from the iron which is absorbed and the iron that comes from deposit organs, which release it into the plasma through ferroportin.[1–3] Their accumulation leads to iron overload that is toxic and can damage tissues and cause cell death by free

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* Corresponding author.
E-mail addresses: euconde@humv.es, condee@unican.es (E. Conde García).

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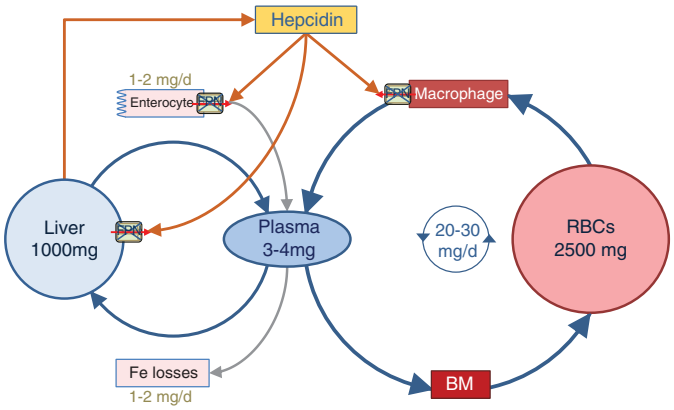

Fig. 1. Body iron homeostasis. The interaction of hepcidin with ferroportin (FPN) controls the main efflux of iron into plasma.

radical formation and lipid peroxidation. For this reason, the circulating iron is never found in free form, it is always attached to other molecules, mainly transferrin, but when concentrations of plasma iron are high and transferrin is saturated, the excess iron is bound to other plasma molecules of low molecular weight such as citrate, acetate and albumin.[2]

The iron in the body follows a cycle consisting of duodenal absorption, distribution through the plasma bound to transferrin and transfer to cells via the transferrin receptor, located in the cytoplasmic membrane, for use in different metabolic processes or for storing it in deposit organs.[1–3] When red blood cells age, they are destroyed in macrophages, mainly in the spleen, and iron is reused after passing through the plasma (Fig. 1). Foods containing ferric iron which, after being reduced to the ferrous form, it is absorbed by duodenal enterocytes and subsequently released into plasma through ferroportin (Fig. 2).

Regulation of iron homeostasis. Hepcidin-ferroportin axis

Hepcidin is the main hormone that regulates iron metabolism. It is synthesized in the liver and its main mission is to control the arrival of iron in plasma from food through enterocytes, macrophages, which contain the iron coming from recycled senescent red blood cells, and that released from the deposits (Fig. 2). *Ferroportin* is responsible for the efflux of iron from enterocytes, macrophages and hepatocytes into the plasma. Hepcidin binds to ferroportin for its destruction by endocytosis into the cell's lysosomes resulting, on the one hand, in a hyposideremia by lowering the iron transferred to the plasma and, on the other hand, to the accumulation of iron as ferritin enterocytes, macrophages and hepatocytes.[1–3] The control of iron homeostasis by hepcidin is a classic endocrine regulation system; in the words of Ganz, the relationship of hepcidin with iron is similar to that of insulin with glucose.[4] Hepcidin is therefore the principal regulator of iron and plays a key role in all its abnormalities, whether having to do with deficiency or excess. Hepcidin deficiency causes iron overload, while its excess favours iron sequestration in the liver and macrophages and contributes to the development of iron deficiency anaemias or because of its misuse in anaemia of chronic disease.[5] In these cases, a functional iron deficiency anaemia occurs because iron reserves are not available for erythropoiesis.[5,6] Increased hepcidin also occurs in chronic inflammatory processes by an increase in IL6, which also represents a host defence mechanism against infection by limiting the availability of extracellular iron to microorganisms.[5] Hepcidin production is negatively regulated by erythropoiesis through mediators that prevent its production when iron is required for haemoglobin synthesis.[5] Hepcidin is an acute phase reactant that responds to a variety of inflammatory mediators and signals that activate transcription through different signalling pathways.[5]

Regulation of hepcidin expression

Hepcidin, encoded by the gene HAMP, is the hormone that regulates iron metabolism. It is a 25-amino acid peptide produced by hepatocytes interacting with the ferroportin found in the cell membrane of enterocytes, macrophages and hepatocytes.[7] Regulation of hepcidin is a multifactorial process involving different stimulatory and inhibitory signals which, in various ways, control its final transcript.[7,8] Hepcidin is regulated by plasma iron through a *feedback* mechanism which involves intra and extracellular iron sensors coupled to one or more signal transduction pathways.

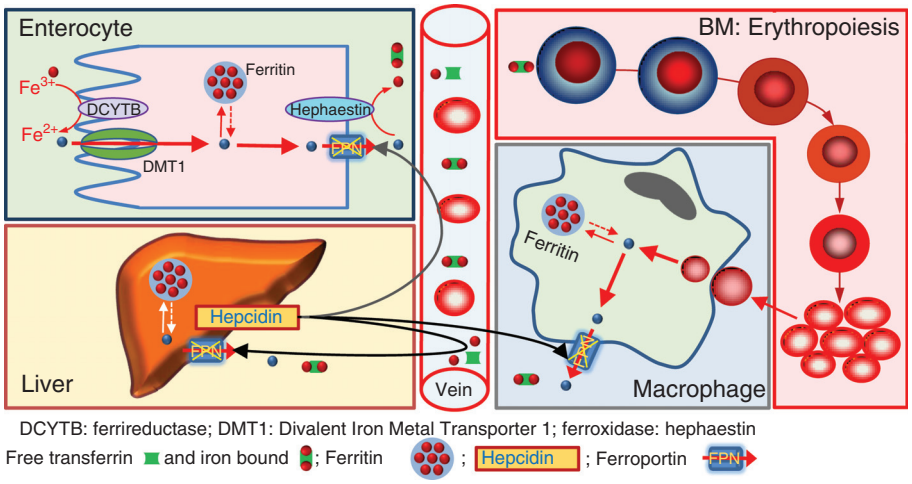

Fig. 2. Dietary iron is absorbed by duodenal enterocytes. Nonheme iron occurs primarily in the ferric state (Fe 3+) in the intestine and is reduced to ferrous iron (Fe 2+) by the action of ferrireductases, especially duodenal cytochrome b (Dcytb). Ferrous iron passes through the duodenal enterocytes of the divalent metal transporter-1 (DMT1). Once in the enterocyte, the ferrous iron can be stored in it as ferritin or can be released into the bloodstream through ferroportin (FPN). Ferrous iron is oxidized by a ferroxidase identified as hephaestin, which after converting into ferric iron, it binds to transferrin and thus circulates in plasma. Furthermore, senescent erythrocytes are phagocytosed by macrophages, primarily in the spleen, but also in the liver and the bone marrow (BM). During erythropoiesis, erythroblasts acquire iron for haemoglobin synthesis from transferrin via transferrin receptors. Excess iron is stored in the liver and in macrophages as ferritin, which is oxidized to hemosiderin. Hepcidin plays a key role in the release of iron from the deposits depending on the requirements (e.g.: increased erythropoiesis, etc.).