Artykuł przeglądowy *Review*

Influence of hepcidin on iron metabolism

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Summary

The main role of iron is being part of haemoglobin, whose level it stabilizes; however, iron also plays a very important role in immunological processes and the metabolism of the organism. Hepcidin is a peptide hormone. It was first isolated from human blood and urine, and its release was attributed to the liver. A failure to produce hepcidin is related to iron overload, while its excessive production to anaemia caused by iron deficit. The releasing of hepcidin also affects hypoxia and inflammation through inhibiting these processes in patients with haemochromatosis. There are three forms of the regulation of the iron level: the first is a regulation in cellular storages, the second is erythropoiesis and the third is a dietary regulator. Hepcidin was identified as a regulator which communicates the level of iron reserves in the organism to intestine cells responsible for the absorption of iron. In inflammatory conditions, when the organism wishes to cause alimentary iron deficit, hepcidin production increases even a hundred fold, thus leading to anaemia. Hepcidin is also a stimulator of inflammation as an antibacterial factor produced in the liver parenchyma. It decreases the absorption of iron in the intestines and increases the secretion of iron to the reticuloendothelial system. Experiments on animals deprived of hepcidin and animals with its excess make it possible to understand iron homeostasis and confirm the role of hepcidin as a hormone regulating iron metabolism.

Keywords: hepcidin, iron, absorption, anaemia

Iron in human and animal organisms is considered as one of the microelements necessary for the functioning of cells (1, 14). Iron is a basic component of molecules transporting and storing oxygen, as well as many enzymes, which need energy generation. It is also needed in the production of indirect metabolites and plays an important role in both specific and non specific immune processes of the organism (2, 5, 10). Iron is necessary for neutrophiles in their bactericidal action for the production of hydroxide radicals (5). The toxic effect of free iron is ascribed to the production of reactive free radicals (1, 8, 15). It was observed that an excess of iron predisposes the organism to the development of intracellular pathogens and blood pathogens, and even its small excess reduces the host's immunity to diseases (9, 10).

The organism possesses a system that maintains iron homeostasis, because both its excess and deficit are associated with cellular dysfunction. The regulation of iron absorption from the intestine and its salvage from old erythrocytes is of crucial importance for balancing the metabolism of that element (18, 21, 22).

The liver plays a fundamental role in maintaining iron homeostasis; it is the main place of storage for an excess of iron in the organism (34). Hepcidin, which is produced in the liver, plays an important role in the communication with cells responsible for the absorption of iron and thus maintains iron homeostasis, functioning as a powerful negative regulator of the absorption and mobilization of that element (3, 4, 17, 19, 33).

Discovery of hepcidin

Hepcidin was isolated from human urine and blood by two independent research teams as an antibacterial peptide (16, 26). In the last seven years the central role of hepcidin as a hormone regulating the iron level and the mediator of the inborn immunity in humans and animals was explained (10, 21). Lack of hepcidin expression caused iron overload, while its excess resulted in anaemia caused by iron deficit. The hepcidin level decreased in animals fed an iron-deficient diet (18, 19). In animal models, hepcidin is mobilized by inflammatory conditions and iron excess (10, 19, 21). The urinary excretion of hepcidin was increased in patients with an increased iron uptake, infections or inflammatory diseases (21).

Structure of hepcidin

The predominant hepcidin form in humans is a peptide containing 25 amino acids but also shorter peptides of 22 and 20 amino acids were observed (10, 13, 21, 27). Some artificial forms of hepcidin have already been synthesised (10). In the human organism there is only one copy of the gene of hepcidin expression while in mouse it was found in two places. That peptide contains four intrachain disulphide bonds and eight cisteine

molecules which are the common feature in various species, while the structure of hepcidin is similar in humans, mice and even fish (10, 22, 26, 27, 31). Recent research suggests that kidneys and the spleen can also produce hepcidin (29, 30).

Role of hepcidin in the absorption of iron from the alimentary tract

Hepcidin was isolated from the liver of mice which were administered carbonyl iron compounds and from the control group comprising mice with the spontaneous iron loading (knock-out mice). The level of hepcidin mRNA increased in the livers of mice from the first group and the amount of mRNA was directly connected with the iron content in the liver, thus proving the dependence of mRNA induction on the dose of carbonyl iron compounds in mice. In the knock-out mice fed a feed with a low iron content a decrease of hepcidin expression was observed. It was noted that the livers of the knock-out mice completely lacked hepcidin, which was responsible for the hyperabsorption of iron, leading to its excess, but also for a cascade iron release from macrophages, leading to the situation when macrophages in the spleen were completely devoid of iron. The conclusion from these experiments was the definition of hepcidin as a hormone regulating the iron level; its overproduction was found to be responsible for anaemia associated with a deficit of that element (10-12, 18).

Role of iron in hepcidin formation

While investigating the response of the liver to iron excess, Pigeon et al. (27) discovered the hepcidin mRNA mainly situated in hepatocytes. As confirmed by Zhang et al. (34), hepcidin was mobilized as a result of an excessive iron content in the diet as well as the parenteral administration of iron. The authors (7, 20, 22-25) investigated the processes of regulating the iron level and they reached the conclusion that the hepcidin level increased with iron overload and decreased with iron deficit.

Role of hepcidin in iron transportation

Molecules which mediate in the transportation of iron unconnected with heme in erythrocytes (3) were discovered in a study on mutations causing microcyte anaemia in mice, rats and fish or the expression of cloned oocytes in frogs (10, 11). In erythrocytes, iron can be stored in the form of ferritin or transferred to the alkaline surface of the cell; from there it is transported outside through ferroportine, reoxidated by hefestine and taken by transferrin to be disposed of in the tissues.

It appeared in the investigations performed that in the case of an iron-deficient diet the absorption of iron as well as the concentration of iron transporters increase; that increase was correlated with a decrease in hepatic hepcidin mRNA; consecutive studies showed significant negative corelation between hepcidin's mRNA level and the level of iron transporters (10).

It was observed in rats that after changing their feed from iron rich to iron poor their iron absorption increased, which was accompanied by an increase of the expression of duodenal reductase of iron and duodenal transport proteins. These changes were correlated with a decrease of hepcidin and a decrease of the organism's saturation with transferrin. The results of the experiment demonstrate that the cellular iron concentration is not the only factor affecting the hepcidin release. In the investigations described, hepcidin seems to be a significant factor in the regulation of iron management in the organism. Each pathological disturbance leading to a change in the hepcidin level results in an excess or deficit of iron (23).

Inflammatory condition and bacterial infection and an increase of hepcidin

Bacteria are unable to store iron and rely on its presence in the host's tissues. That causes an interesting system of antibacterial defence in the attacked organism in the form of the so-called nutritional immunity, i.e. the generation by the human or animal organism of the appearance of hypoferremia in order to inhibit the development of infection; that is why an inflamatory ondition causes a decrease in the level of iron in the plasma but it is not clear what mechanisms or factors are responsible. Immunity to infection partly depends on the result of a battle for iron between the host and the attacking bacterium (5).

The relation between the induction of hepcidin and inflammatory conditions in humans confirms the thesis about the key role of hepcidin as a mediator in anaemia and inflammatory conditions (3, 21).

Hepcidin is induced by an elevated iron content and inflammatory conditions, which gives an impulse to the small intestine to reduce iron absorption and to macrophages to release iron (21).

In inflammatory conditions, this leads to a decreased absorption of iron in the small intestine and an increased release of iron to the reticuloendothelial system (24, 27). Inflammation accompanies anaemia in the course of chronic diseases. That anaemia is characterized by a reduction of the survival rate of red blood cells and a decrease of iron flow from macrophages and enterocytes (18).

In humans the urinary excretion of hepcidin increases significantly in patients with iron overload, during inflammation and in the course of diseases with an inflammatory background (21). A reply to stress and inflammation in the form of hepcidin probably reflects the primary antibacterial function of that peptide (12).

Ganz (10) reports results of investigations in which the production of hepcidin mRNA was increased 4500 times through the infection of fish with a pathogen; at the same time that factor caused a decrease of the iron content in the serum. A similar relationship was observed in investigations on inflammatory conditions in humans: when the organism wishes to induce the alimentary deficit of iron, the production of hepcidin increases even 100 times, which leads to anaemia. Thus it could be summed up that the production of hepcidin by hepatocytes is regulated by inflammatory conditions caused by bacterial infection.

Effect of anaemia and hypoxia on the reduction of the hepcidin content

Anaemia is a sign which is characterized by disorders in the response of erythrocyte precursors to erythropoietin, a shortening of the erythrocyte survival rate and the defect in iron absorption as well as disorders of its retention with the help of macrophages. These effects disturb the availability of iron to cells which are erythrocyte precursors (32).

Hepcidin plays a most important causal role in the occurrence of anaemia observed in the course of chronic diseases (32). Anaemia and the accompanying hypoxia are adequate signals causing an increased iron absorption in the intestines (3, 6, 10, 21, 24). These impulses decrease hepcidin production and thus reduce its blocking of iron absorption and iron release by macrophages, which results in the availability of iron for erythropoiesis (3, 10, 24, 28, 32, 33).

It was observed in experiments that in the case of a decreasing partial pressure of oxygen and hypoxia there was a drastic decrease of the hepcidin level (24). Thus it can be assumed that the state of hypoxia induces erythropoiesis and that the regulation of the expression of the hepcidin gene occurs through erythropoietin (18).

Conclusion

Hepcidin, an identified regulator of the iron level proved to be an indicator of the iron level in the organism. It is also a hormonal factor necessary for erythropoiesis, and in iron metabolism it is a modulator of its intestinal absorption. First hepcidin was isolated from human blood and urine as an antibacterial peptide, and to a high degree its release was attributed to the liver. The hepcidin content in mice, rats and fish increases during an acute phase of reaction to an impulse (19). The hepcidin level decreased in mice fed an iron deficient feed and increased in mice fed a diet rich in that microelement. These observations helped to understand the role of hepcidin as a signal limiting the intestinal absorption of iron.

Hepcidin may be the main peptide hormone regulating the iron level, the key mediator of anaemia associated with an inflammatory state as well as between immunity and iron metabolism. Investigations on the molecular mechanism of hepcidin activity may change our understanding of the regulation of iron transport and may lead to new therapies of the anaemia of inflammation (10, 19).

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