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HEPCIDIN EXPRESSION AND ACTION ARE MODULATED BY THE INFLAMMATORY RESPONSE, WHICH CAUSES IRON DEFICIENCY ANEMIA AND INTERFERES WITH ENERGY SYNTHESIS

Flávio Bachini[1], Anibal Monteiro de Magalhães Neto[4,5], Marcio Vinicius de Abreu Verli[2], Adriana Guimarães[3], Cristiane Pessoa de Andrade[3], Fabiana Dos Santos Barroso[3], Suellen Guarani Borges da Silva[3], Eva de Fátima Paulino[3], Douglas Daniel Costa Santiago[2], Jaqueline Santos Silva Lopes[2] and Luis Carlos Oliveira Gonçalves[2,3,5]*

[1]Postgraduate Program in Neurology - UNIRIO, Brazil.
[2]Postgraduate Program in Health Sciences – UFMT, Brazil.
[3]Graduation in Nursing – UNIRJ, Brazil.
[4]Postgraduate Program in Basic and Applied Immunology and Parasitology – UFMT, Brazil.
[5]Protein Biochemistry Laboratory – UNIRIO, Brazil.

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***Corresponding Author**
Dr. Luis Carlos Oliveira Gonçalves
Protein Biochemistry Laboratory - UNIRIO, Brazil.

ABSTRACT

Hepcidin was first described in mice. It is a peptide hormone composed of 25 amino acids, synthesized in the liver and detectable in blood and urine. This is a narrative review of the literature about the role of hepcidin in the regulation of energy and iron metabolism. Exercise, diseases and aging can cause inflammatory processes. These processes increase the synthesis of pro and anti-inflammatory cytokines. Some cytokines such as IL-6 stimulate hepicidin expression and activity. With its increased activity, this polypeptide stimulates the uptake of iron by macrophages and decreases its absorption in the diet. This aforementioned process causes iron deficiency anemia, which affects the synthesis and degradation of universal metabolic precursors. This whole situation leads to a decrease in the synthesis of the heme group, due to a decrease in the production of intermediates in the Krebs cycle and low bioavailability of iron and other divalent metals. Exercise is a stimulant of inflammatory mediators that signal the expression of systemic hepcidin and proteins that transport iron in BBB. Therefore, the inflammatory process and peripheral iron can influence hepcidin expression and reduce iron overload in the CNS. Several pathologies associated with the nervous system have shown a correlation with

hepcidin levels and iron metabolism, including amyotrophic lateral sclerosis, multiple sclerosis, Alzheimer's disease and restless leg syndrome. The future perspective suggests that the next studies look for a correlation between the levels of hepcidin, caused by inflammatory processes, and diseases related to the nervous system.

KEYWORDS: Metabolism, Cytokines, Neurodegenerative Diseases, Anemia.

INTRODUCTION

The structure, regulation, expression and role of hepcidin were first described in studies with mice, in which ultra-filtered plasma was isolated and called an antimicrobial peptide expressed by the liver (LEAP-1).[1,2,3] Then, it was proposed that mice without the LEAP-1 gene had shown an action on iron metabolism.[3,5]

Thus, the loss of the gene that encoded the transcription factor resulted in an overload of serum iron, similar to human hereditary hemochromatosis. At this time, the action of hepcidin on iron metabolism has been proposed.[1,2,3]

Hepcidin is a circulating peptide hormone composed of 25 amino acids, synthesized in the liver and detectable in blood and urine.[4,5] The number of hepcidin-related research has increased considerably since it was proposed, and its role has been extensively investigated by scientific community[11,12] seeking, with enormous interest, to quantify the circulating levels of hepcidin in clinical samples.[12]

Hepcidin hormone presents itself as the main regulator of iron homeostasis in the body and possibly a mediator of inflammation, anemia and chronic diseases. As the main systemic regulator of iron homeostasis, hepcidin regulates the storage and use of this mineral in the body,[13,14,15] being the mediator in the iron absorption cycle among the liver, the intestine and macrophages.[16,17]

Iron is an essential micronutrient for erythropoiesis and energy metabolism. Its reduction and depletion are closely related to anemia. Anemia is classically caused by hematuria, hemolysis, sweating, gastrointestinal bleeding and the imbalance between menstrual flow and iron intake in female athletes.[18,19] On the other hand, the regulation of hepcidin depends on iron itself, inflammation, hypoxia, transferrin and erythropoiesis.[20] This hormone affects iron metabolism by internalizing and degrading ferroportin (FPN1), which can result in reduced iron efflux in the plasma in the small intestine, liver and macrophages.[21] In addition,

the divalent metal ion transporter 1 (DMT1) transporter absorbs non-heme iron at the apical edge of enterocytes, which, through duodenal cytochrome B (DcytB) - an iron reductase - reduces iron ferric status (Fe3 +) for ferrous (Fe2 +).[20]

Determining hepcidin concentration can be useful to diagnose different types of anemia, such as iron deficiency anemia, which is characterized by a low level of this hormone. Hepcidin dosages may complement the current indicators most used to assess the body's total iron stores, such as serum ferritin[22,23,24], the transferrin receptor, the transferrin saturation and zinc protoporphyrin.[24]

These indicators are used to control iron stores in diseases, aging and in athletes. In diseases and aging, iron accumulation was observed by iron transporters in the blood-brain barrier (BBB) and in neuron-astrocyte-glial cells.[25] The increase in the iron content in the CNS has been identified as one of the causes of motor deficit and cognitive impairment in Alzheimer's disease, in the brain of cirrhotic patients related to the hepatitis B virus. [26, 27, 28, 29] Additionally, in moderately trained male runners, it has been shown that, inflammation induces the increase of hepcidin production 3-6 hours after the marathon.[30]

Hepcidin activity affects the serum homeostasis of iron and can cause iron anemia deficiency: a usual problem in elite athletes, but it has not been postulated about its performance in the CNS. Differences between gender in hepcidin production and iron status were also observed in study models in mice and humans.[31,32] Therefore, this review will discuss the role of inflammation in post-exercise hepcidin production in elite athletes. In addition, hepcidin production and iron metabolism in the CNS have not been studied in elite athletes. However, it has been shown that altered iron metabolism can affect the CNS and promote motor deficit and cognitive impairment. Accordingly, another point of this review is to postulate the effect of hepcidin on iron uptake by the brain. The main objective was to make an unsystematic and narrative review of the literature about the function and applicability of the hepcidin polypeptide in the maintenance and regulation of energy and iron metabolism.

Hepcidin

Hepcidin is found in three forms: with 25, 22 and 20 amino acids[33]. In its active form in the circulation, it binds to ferroportin, making its internalization and lysosomal degradation.[34] Present on the cell surface of placental cells, macrophages, hepatocytes and enterocytes, ferroportin is responsible for the iron conduction from the intracellular medium to the plasma,

functioning both as an iron efflux channel regulated by hepcidin, and as a hepcidin receptor, thereby promoting a reduction in iron plasma levels by decreasing its intestinal absorption, releasing by macrophages and hepatic stores.[4]

In a study on the hepatic response to iron overload, where the relation between hepcidin and iron was pointed out, two stimuli were indicated: iron overload and lipopolysaccharides; they both induced hepcidin production.[35] Infections also stimulated hepcidin, causing inflammation anemia, aiming to decrease the iron availability for pathogenic agents.[36]

Hepcidin production is induced by inflammatory cytokines, mainly by IL-6, indicating that the stimulus that hepcidin undergoes during inflammation is an indirect effect.[7,8] Other inflammatory cytokines also stimulate hepcidin such as IL-1α, IL-1β and bone morphogenetic proteins (BNP).[37] Thus, a study with two groups was described: obese and non-obese women. In this study, it was found that, the detectable accumulation of iron in the liver and abdominal adipose tissue of women with obesity was minimal, therefore, they had higher levels of hepcidin. However, it was observed that, the source of hepcidin excess appears to be adipose (inflammatory) tissue and not the liver (iron stores). Thus, it was found that, hepcidin levels were elevated in obese women, indicating the presence of iron deficiency in these patients.

Hepcidin and Iron Metabolism

Iron Balance is important for physical performance and health maintenance.[38] In recent years, many studies have been done seeking to advance the understanding of the genetics of iron metabolism and numerous new proteins, including hepcidin. The regulation of iron homeostasis occurs by two main mechanisms: one is intracellular, depending on the amount of iron that the cell has; and the other is systemic, in which hepcidin plays a fundamental role.[39] It was established that hepcidin would be a negative regulator of iron metabolism, being synthesized by the liver in the form of a propeptide and, after that, processed and secreted in the circulation where it is detected in plasma and urine.[9]

In recent studies with cell cultures, hepcidin action in the intestinal absorption process and in macrophages, hepatocytes and enterocytes has been demonstrated. During the intestinal absorption process, inhibition of iron uptake by enterocytes occurs by inhibiting the transcription of DMT-1 induced by hepcidin, which is an important receptor protein for iron absorption in the enterocyte epithelium, while levels of FPN1 in these cells do not change.

On the other hand, in macrophages, hepatocytes and also in enterocytes, ferroportin is the receptor for hepcidin and iron levels are controlled by hepcidin-ferroportin integration. The hepcidin-ferroportin complex is internalized in the domains of the basolateral membrane of macrophages and ferroportin is broken down, blocking the iron outflow from these cells. So, hepcidin effect is cell-dependent.[40] As a consequence, iron accumulation occurs in hepatocytes and macrophages, causing a reduction in the passage of iron to plasma, resulting in low transferrin saturation for the development of erythroblasts.

Hepcidin and Inflamation

Inflammation is a natural physiological process that occurs in response to different stimuli such as infections, physicochemical and antigenic changes or traumatic damage, with the consequent production of anti-inflammatory cytokines in response to this inflammation.[41,42,43] Inflammation leads to an increase in several cytokines, including IL-6, which is primarily responsible for hepcidin synthesis.[7,8]

The binding of IL-6 to its receptor, on the surface of the hepatocyte, signals the phosphorylation of the *Signal transducer in activator of transcription* 3 (STAT3) to occur through the protein *Janus kinase* (JAK)[34,44] and its translocation to the nucleus, where it binds to the HAMP gene promoter,[45] and promotes the transcription of this gene and the synthesis of hepcidin. The ultimate goal is to limit the iron available to infectious agents by inflammation.[7,8] As in iron-dependent pathogens cases, in which the defense mechanism is to promote iron deficiency anemia in order to reduce the release of iron by macrophages.[47,48,49]

Other inflammatory cytokines do not appear to stimulate hepcidin production; such as TNF-α, which apparently prevents hepcidin production from occurring.[46]

Hepcidin and Exercise

Hepcidin production depends on exercise-induced inflammatory mediators. Therefore, the intensity and duration of exercise can affect iron metabolism differently. It has been documented that, IL-6, for example, regulates hepcidin activity. These inflammatory mediators interfere with the control of iron-transporting proteins. These proteins are expressed in the liver and brain, such as: TRF1, FPN1, DMT1, Dcytb and binding proteins to responsive elements to iron 1 and 2 (IRP1, IRP2).[50, 51, 52, 53]

Acute exercise stimulates the production of IL-6 which signals the expression of hepcidin in the liver.[52] The first study that explored the relationship between acute exercise and production of urinary hepcidin proposed that women could respond and could not respond to the peptide hormone of acute phase and they showed a peak of hepcidin 24 hours after the marathon (lasting around 4-5 hours).[51] It has recently been reported that endurance athletes can reach their peak of serum hepcidin 3 hours after exercise (60 or 120 minutes of exercise with the same intensity), remaining elevated between 6 and 9 hours and returning to baseline after 24 hours.[53] It seems that in acute exercise the time on the peak of serum hepcidin is different from the peak of urinary hepcidin in female athletes.

It has been shown that, the production of serum hepcidin during exercise can reach its peak 3 hours later. However, whether sustained hepcidin production during chronic exercise can induce inflammation anemia needs to be clarified. It is necessary to assess the inflammation, hepcidin, iron regulatory proteins to understand iron status and absorption during a long-term exercise. Chronic exercise in athletes may increase the risk of depleting iron stores, not through inflammation/hepcidin, but through iron itself.[54,55] In this sense, 10 weeks of moderate exercise can promote an increase in the absorption of duodenal iron in mice due to increased expression of DMT1 and iron absorption in the epithelium in the enterocytes. On the other hand, the increase in hepcidin induced by the inflammatory process negatively regulates iron in the blood, allowing to increase the expression of FPN1 and reducing the transfer of iron to the circulation.[56] In addition, six weeks of moderate resistance training increased hepcidin production which reduced the release of iron in the blood, increasing the mobilization of iron by the degradation of senescent erythrocytes and maintaining iron homeostasis in iron-deficient mice.[57] Therefore, iron levels are maintained mainly by recycling senescent erythrocytes in the bloodstream..

In the strenuous exercise, different responses were shown according to the duration. During five weeks of strenuous exercise, inflammation increases the expression of hepcidin, which could reduce iron absorption after exercise, due to the reduction of DMT1 and FPN1, which can contribute negatively to the production of erythrocytes and anemia in mice.[58] In addition, 10 weeks of strenuous exercise were responsible for the exercise-induced anemia, there were no changes in the expression of DMT1 and FPN1 and in the production of hepcidin, to compensate for the low iron absorption, there is an increase in iron mobilization of the ferritin trying to maintain iron levels. This mechanism may be responsible for iron

deficiency anemia.[56] Knowledge about how exercise interacts with iron regulation is still up for debate, but it can be argued that long-term strenuous exercise increases hepcidin production and affects iron stores and regulatory proteins, resulting in iron deficiency anemia. On the other hand, moderate exercise can increase iron absorption, which reduces hepcidin activity.

Hepcidin activity classically depends on iron status and iron inflammation. As noted, IL-6 precedes the peak of hepcidin.[53] After training, the peak of hepcidin reached 3 hours later and began to return to baseline. To date, the highest peak of hepcidin in serum and urine in female athletes has not been clearly established. Measurements of the hormone hepcidin have been proposed before and after exercise, 3, 6, 9 and 24 hours after high-intensity exercise in response to inflammation.[53,59] In addition, serum hepcidin assessments were also used in pre- and post-training and recovery of one week or 10 days.[54,60] And a single measurement of serum hepcidin comparing two groups: high school runners and low-level female exercises.[55] These different protocols can be difficult to make conclusions about hepcidin serum activity and IL-6 production. In addition, these studies considered regular menstrual cycles, but none have been evaluated considering the use of oral contraceptive pills, which could affect IL-6 production and hepcidin activity. Different phases of single-phase use of the oral contraceptive pill have not been shown to alter the production of IL-6 or hepcidin. Therefore, in acute or chronic exercise, hepcidin activity in female athletes and the influence of female hormones on IL-6 and hepcidin production needs to be better established.

Hepcidin and Blood Brain Barrier

Strenuous exercise can increase hepcidin activity in response to IL-6 production. In this sense, elite athletes are constantly training in higher efforts and iron deficiency anemia is a current concern related to erythropoietic demand. Reduced erythrocyte production and iron-related parameters can impair brain performance and function.

The blood-brain barrier (BBB) is a specialized system that protects the brain against plasma proteins, metals and polar substances.[61] Thus, systemic hepcidin is not responsible for iron poisoning in the brain, due to the impermeability of the blood-brain barrier to hepcidin.[62] Hepcidin and iron were found within the CNS: in the olfactory bulb, cortex, hippocampus, amygdala, striatum, substantia nigra, thalamus, hypothalamus, midbrain, cerebellum, bridge, spinal cord and in the dorsal root ganglia of the peripheral nervous system.[61,63] Therefore,

hepcidin levels in the cerebral cortex, cerebellum, midbrain and bridge are significantly higher than in the hippocampus.[64]

BBB is impervious to hepcidin production. However, it has been shown that hepcidin production in the CNS can be induced by acute-phase protein and cytokines. Intramuscular administration of turpentine oil (OT) at a dose of 5 ml / kg body weight increased the acute-phase response mediated by cytokines in the hippocampus that positively regulated transferrin and TRF1 (which encodes the receptor of transferrin 1).[50] In addition, increased levels of iron regulatory protein 1, TRF1 and hepcidin were also mediated by IL-1β or TNF-α in the midbrain neurons.[65] Thus, these cytokines and acute phase changes may regulate the uptake of iron in the brain and the differences between regions in terms of hepcidin activity.

Hepcidin does not exceed BBB, but it can regulate the iron which enters in the cells by regulating iron transporters in BBB, neuronal and glial cells, as it is done in the intestine, liver and recycled iron from macrophages.[50, 57, 65, 66] Hepcidin can decrease cAMP messengers (via AMP-kinase A cyclic protein) and PKA (kinase A protein) that reduce the expression of iron transporters, DMT1 and FPN1 in BBB and glial endothelial cells.[61, 67] The main route for the uptake of iron by the brain is probably through transferrin / TRF1.[68]

It has been shown that the increase of hepcidin may directly decrease the expression of ferritin / TRF1 and NTBI (unbound iron to transferrin) in the endothelial cells of the BBB, showing that hepcidin may protect the brain from iron overload.[68] Acute exercise can increase hepcidin responses, however, cumulative training sessions do not affect hepcidin production.[53, 54] To date, no study has evaluated whether exercise can increase hepcidin production and affect iron transporters in endothelial cells..

It is known that, exercise induces to the inflammatory process and the increase of hepcidin outside the CNS. In the CNS, the inflammatory process and hepcidin are under debate about how they affect areas of the brain. So far, hepcidin injection in the left ventricle has been able to increase DMT1 and decrease FPN1 in the hippocampus and cerebral cortex, and the accumulation of iron is the consequence.[69] In addition, treatment with inflammatory mediators (IL-1β, TNF-α, IL-6) increased hepcidin production and culminated in the positive regulation of DMT1 and negative regulation of FPN1, leading to the accumulation of iron in the midbrain neurons and hippocampus.[65,66] The inflammatory process and hepcidin regulate iron regulatory proteins to maintain iron homeostasis in the brain and cerebrospinal fluid.[50]

Iron homeostasis is modified by inflammatory stimuli in many regions of the brain. These brain regions are composed of cells, such as: neurons, astrocytes and microglia. These three types of cells have already been exposed by inflammatory stimulus (IL-6, TNF-α and LPS) for 18 hours. Iron accumulation was observed in neurons and microglia, but not in astrocytes due to the increase in DMT1 in cells of three types and the decline in FPN1 in neurons. And hepcidin decreases FPN1 6h later in these three cells, which aggravates the accumulation of iron in the brain.[66]

Inflammation involves not only cytokines, but also lipopolysaccharide (LPS) in response to infection. LPS can induce increased levels of hepcidin and affect the brain.[66] Peripheral LPS induces mRNA and the protein of hepcidin and in the substantia nigra and cortex, not directly because LPS is unable to cross the BBB, but probably through IL-6.[61] In a similar mechanism, the peripheral stimulus of LPS can also influence the choroid plexus to express hepcidin. In response to the LPS injection, the peripheral signaling complex of IL-6 and BMP (bone morphogenetic protein) increased the expression of SMAD4 and STAT3 mediators in the expression of choroid plexus hepcidin.[69,71] Therefore, LPS can induce changes in the expression of iron regulatory protein and increase the expression and production of hepcidin in the brain.

Exercise is a stimulant to increase inflammatory mediators that signal the expression of hepcidin. It is still under discussion how acute exercise alters iron metabolism. So far, the serum (3h) and urinary (24h) hepcidin peaks are different in female athletes in acute exercise. In addition, long-term strenuous exercise increases hepcidin production and decreases iron stores and regulatory proteins, resulting in iron deficiency anemia. Elite athletes are trained in high effort and depend on parameters related to iron and erythrocyte production to maintain performance. The inflammatory process and hepcidin regulate iron regulatory proteins to maintain iron homeostasis in the brain / cerebrospinal fluid, liver, intestine, macrophage.[21,50] But we still don't know if the production of IL-6 during exercise can cross the BBB and affect the metabolism of iron in brain cells. Another point to be taken into account is female athletes who usually have iron deficiency anemia and iron supplementation is considered to increase the synthesis of blood cells. Increasing the inflammatory process and hepcidin production can affect the iron transporters in endothelial cells in the BBB. In keeping with these ideas, it is important to consider how strenuous exercise and iron supplementation can affect the absorption of iron in the blood and central nervous system.

Hepcidin and Citric Acid Cycle

For several decades, researchers have sought to elucidate and identify possible interferences of metabolic pathways, aiming to understand and propose therapies for various diseases, both acute and chronic. Most of these diseases induce an inflammatory condition, local or systemic, which can compromise homeostasis.

Initially comprising fundamental problems, such as characteristics and forms of interaction between atoms, electron transfer, part of the architecture and the long-term evolution of metabolism and the biosphere and other topics that underlie a modular decomposition of the carbon fixing that responds across all known diversity, especially in terms of unique adaptations to chemically simple variations in the abiotic environment.[72]

From the knowledge that involves metabolism, in a fractional and continuous way, the understanding of known metabolic pathways arose and revolutionized. Regarding hepcidin, recent findings have shown that inflammatory processes, generated by several factors such as diseases, acute and chronic stress, high intensity exercise, among others, increase the expression and action of this polypeptide, which by inducing an increase in iron uptake by macrophages and decreasing uptake of this and other metals by divalent metal transporters in the intestine causes iron deficiency anemia.[13, 14, 15, 16, 17, 20]

It has recently been identified that this iron deficiency anemia has a direct influence on the appearance of anemias and interferes with the synthesis and degeneration of universal metabolic precursors, modulating the energy production in the citric acid cycle.[73]

Hepcidin and Neurology

Iron plays essential roles in the central nervous system. However, how the level of iron is regulated in brain cells, including glia and neurons, remains to be clarified.[74]

Hepcidin appears as a new factor in brain iron homeostasis. Inflammation and iron load induce hepcidin expression in the brain. The most important source of hepcidin in the brain is glial cells. The role of hepcidin in brain functions has been observed during iron neuronal load and cerebral hemorrhage, where abundant hepcidin secretion is related to the severity of brain damage. This damage can be reversed by blocking systemic and local hepcidin secretion.[75]

Previous studies on amyotrophic lateral sclerosis (ALS) have demonstrated an accumulation of iron in the spinal cord and an increase in the concentration of glutamate in the cerebrospinal fluid. Soluble iron can stimulate the release of microglial glutamate and suggests a positive feedback mechanism. This process induces significantly reduced expression of ferroportin in the spinal cord and negative regulation of ferroportin induced by hepcidin in the cell line derived from murine microglia.[76]

Ferritin, hepcidin and transferrin are closely associated with "ferroptosis", a recently discovered form of programmed cell death with promising therapeutic targets.[77]

The accumulation of iron in the brain has been associated with multiple sclerosis (MS). Hepcidin dysregulation is a characteristic of different chronic inflammatory diseases, but has not yet been investigated in MS.[78] Hepcidin and iron-related proteins also appear as a group of serum biomarkers related to the diagnosis of Alzheimer's disease and to the progression of the disease.[79]

A new syndrome known as restless leg syndrome, a condition in which the individual has an uncontrollable urge to move his legs and move them involuntarily, also appears to be associated with dysregulation of iron homeostasis. In patients without drugs and with primary restless leg syndrome, the level of hepcidin is high and may be associated with the clinical severity of this syndrome.[80]

Non-neurodegenerative dementia is also associated with a significant increase in systemic hepcidin. However, data on the status of hepcidin in dementia are scarce and limited to Alzheimer's disease. The association of hepcidin with vascular dementia remains unknown.[81]

Iron delivery to the brain is essential for multiple neurological processes, such as myelination, neurotransmitter synthesis and energy production. Understanding the mechanism by which iron transport across the blood brain barrier (BBB) is regulated is crucial to address the impact of iron deficiency on brain development and excessive iron accumulation in neurodegenerative diseases.[82]

Estudos sugerem um duplo papel da hepcidina na carga de ferro neuronal e na inflamação. Isso é importante, pois a carga neuronal de ferro e a inflamação são processos fisiopatológicos frequentemente associados à neurodegeneração. Além disso, a manipulação

da atividade da hepcidina foi recentemente usada para recuperar danos neuronais devido à inflamação do cérebro em modelos animais e células cultivadas.[83]

Final Considerations

Exercise, disease, aging can generate inflammatory processes, which are characterized as an immune response to infectious, chemical or physical agents. These inflammatory processes increase the synthesis of pro and anti-inflammatory cytokines. Some cytokines such as IL-6 stimulate hepcidin expression and activity. With its increased activity, this polypeptide stimulates the uptake of iron by macrophages and decreases the absorption of this and other metals in the diet, via carriers of divalent metals in the intestine and liver.

This aforementioned process causes iron deficiency anemia, which in turn affects the synthesis and degradation of universal metabolic precursors. This whole situation leads to a decrease in the synthesis of the heme group, due to a decrease in the production of intermediates in the Krebs cycle and low bioavailability of iron and other divalent metals.

On the other hand, exercise is a stimulant to increase inflammatory mediators that signal the expression of systemic hepcidin and iron transporator proteins in BBB. However, BBB is impervious to the production of systemic hepcidin which could increase the iron overload in the CNS. However, it has been shown that hepcidin production in the CNS can be induced by acute phase protein and cytokines. Therefore, the inflammatory process and peripheral iron can influence hepcidin expression and reduce iron overload in the CNS.

Several pathologies associated with the nervous system have shown a correlation with hepcidin levels and iron metabolism, including amyotrophic lateral sclerosis, multiple sclerosis, Alzheimer's disease and restless leg syndrome. The future perspective suggests that the next studies look for a correlation between the elevation of hepcidin levels, caused by inflammatory processes, and diseases related to the nervous system.

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