The Medical Importance of Hepcidin: Review

Hepsidinin Tıbbi Önemi: Derleme

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ABSTRACT

This review aims to study chemical, medicinal and functional properties of Hepcidin. Hepcidin (small bactericidal peptide) is considered a vital regulator of the iron entry in the blood of mammals. Hepcidin, a 25 amino acids long peptide hormone, has antimicrobial activity, especially in urine. Also, many remarkable results exhibited antibacterial, antifungal and anti-candidal activity against multidrug resistance pathogens, *in vitro*. The central of its formation is cells of the liver (hepatocytes). The expression of Hepcidin is low when iron stores of the human body are insufficient.

Key Words: Antimicrobial agent, Anaemia, Iron metabolism, Peptide, Hormone.

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ÖZET

Bu derleme, Hepsidiniin kimyasal, tıbbi ve fonksiyonel özelliklerini incelemeyi amaçlamaktadır. Hepsidin (küçük bakterisidal peptit), memelilerin kanına demir girişinin hayati bir düzenleyicisi olarak kabul edilir. 25 amino asit uzunluğunda bir peptit hormonu olan hepsidin, özellikle idrarda antimikrobiyal aktiviteye sahiptir. Ayrıca, birçok dikkate değer sonuç, in vitro olarak çoklu ilaca dirençli patojenlere karşı antibakteriyel, antifungal ve anti-kandidal aktivite gösterdi. Oluşumunun merkezi karaciğer hücreleridir (hepatositler). İnsan vücudundaki demir depoları yetersiz olduğunda Hepsidin ekspresyonu düşüktür.

Anahtar Sözcükler: Antimikrobiyal ajan, Anemi, Demir metabolizması, Peptid, Hormon.

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INTRODUCTION

Hepcidin is the protein which encoded using the gene of HAMP in humans. It is the key regulator of the entry of Fe (iron) in blood of mammals (12). For the first time, it was discovered serum and urine of human in 2000 (24). It was discovered in samples of human blood ultra-filtrate and urine as a small bactericidal peptide (defensing, and cathelicidin) which called LEAP–1 peptide (liver-expressed anti-microbial peptides) (5,18). The term of hepcidin originated from the synthesis site in the hepatocytes (hep-) and its anti-microbial efficacy (-cidin). It has anti-bacterial (*Staphylococcus aureus*, *E. coli*, *Streptococcus* spp. group B, *Staphylococcus epidermidis*) and anti-fungal efficacy (*Aspergillus fumigatus*, *Candida albicans*, *Aspergillus niger*) (36). However, the present protein is considered one of the key regulators of levels of Fe, it reduces the absorption of iron from the duodenal enterocyte, releasing Fe from the macrophage and its pass through the placenta (10,40). The formation of hepcidin in the hepatocyte can be organized using Fe overload, signals of inflammatory, increased anaemia, erythropoiesis and hypoxia (1).

The chemical composition of hepcidin

Hepcidin, a 25 amino acids long peptide hormone as in Figure 1, is the key regulator of homeostasis of iron in vertebrates (6). The expression of Hepcidin is low when iron stores of the body are insufficient, as in hypoxia or anaemia. The bio-synthesis and expression of hepcidin are frequently induced using inflammation and iron loading (4,30,35).

Hepcidin finds as a pro-hormone (sixty amino acids [aa]), prepro-hormone (eighty-four aa), and hormone (twenty-five aa). Also, twenty-amino acid metabolites of hepcidin find in the urine. 5 N-terminal aa deletion leads to a lack of the function. The prohepcidin conversion to hepcidin is assisted using the pro-hormone convertase furin (41). However, the present conversion may be organized using α-1 anti-trypsin (33). Hepcidin was the closely folded poly-peptide by 32.0% beta-sheet character, and the hairpin structure firmed using four bonds belong to the disulfide bond type. The hepcidin structure was characterized throughout the NMR of solution (20). Studies of NMR exhibited newly pattern to hepcidin: at the ambient temperature, the proteins interconvert between 2 conformations, which could be separately settled using a variation of temperature. The hepcidin solution structure has been detected at 253 K, and 325 K in the super-cooled water. Also, the analysis of X-ray for the cocrystal with Fab showed the structure analogous to the high-temperature NMR structure (21). The HAMP (gene of the human hepcidin) was situated on the chromosome 19q13.1 (24). Also, it was 2637 bp long and consisted of 2 introns and 3 exons (34). The expression of the HAMP gene has been determined generally in the liver, brain, heart, prostate gland, lung, salivary gland, trachea, and tonsils (25). The HAMP encoded the precursor of hepcidin – prepro-hepcidin, which is eighty-four amino acids protein included twenty-four aa leader peptide at the N-terminal, the thirty-five aa proregion, and C-terminal twenty or twenty-five aa mature peptide. Prepro-hepcidin is split to sixty aa pro-hepcidin which is further amino-terminally processed and leads for increasing the hepcidin. However, there were 3 hepcidin forms: twenty aa peptide, twenty-two aa peptide, and twenty-five aa peptide. Also, the 3 forms were discoverable in the urine, but just hepcidin-twenty five and hepcidin-twenty were found in serum of human (38). The hepcidin-25aa structure, which is the primary form of the hepcidin, includes eight cysteine residues linked using the bonds of disulfide (25). Moreover, the hepcidin structure analysis using spectroscopy of NMR exhibited that the current forms of peptide the stabilized simple hairpin using 4 bonds of disulfide between the 2 antiparallel strands. The unusual vicinal disulfide bridge present at the hairpin turn very likely plays important active role (20).

The structure of hepcidin was described by NMR solution which firstly recorded by Hunter et al. who showed that the compact fold of it by beta-hairpin loop, and beta-sheet elements (20). Also, from the dynamic signatures, and calculations of structure in the spectrum of NMR, authors assessed the connectivity of disulfide of cysteine3–cysteine6,4, cysteine2–cysteine7, cysteine1–cysteine8 and the rare vicinal disulfide bond at the cysteine4–cysteine5. Another research of the bass hepcidin verified connectivity the same disulfide and detected the same fold mainly (27). Nevertheless, both kinds of research, have been based on the in-complete information of NMR due to resonances from 2 adjacent cysteines (cysteine-14 and cysteine-13) of the hepcidin, weren't determined, probably because of the exchange broadening. The obtained data of NMR at various temperatures exhibit that the hepcidin shows important conformational dynamics in the solution. The problem that probably occluded last studies of NMR, the presented information here exhibit that these dynamics can be almost completely resolved using temperature variation, yielding 2 distinct hepcidin structures, 1 at 253 K and other at 325 K in the supercooled water, additionally to infer bonds of disulfide from calculations of structure. The argument based on the probabilistic interpretation of data of NMR has been presented, which unequivocally demonstrates the same connectivity as received from the chemical analysis (21).

The synthesis of hepcidin

Hepcidin is a peptide composed of twenty-five amino acids and contains four disulfide bridges (20) (Figure 1). This peptide was discovered newly, as it is included in the regulation of Fe, and many Fe disorders, like Fe deficiency anaemia, hemochromatosis, chronic disease anaemia, and inflammatory anaemia. It also has antimicrobial activity. It is an element of the innate immune system (8,13,31). Hypsidine is synthesized in the liver, kidneys and in some tissues of the body (26).

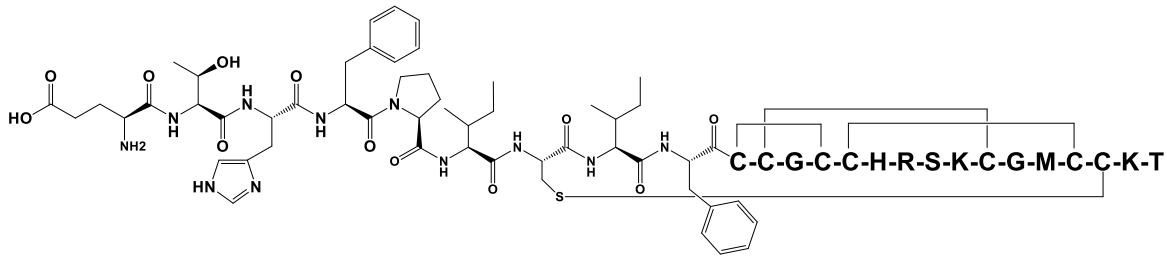


Figure 1. Structures of human hepcidin.

Several attempts were made to prepare hepcidin and its derivatives by (9), the prepared hepcidin in addition to four derivatives of the β-defensins family (Figure 2), which contains disulfide bonds using the synthesis of the solid-phase peptide by the fluorenylmethoxycarbonyl chemistry. This synthesis process is useful compared to the production of active antimicrobial peptides because of the rapid production and the fact that these peptides are toxic to microorganisms.

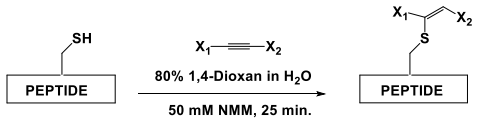
Hepcidin is used to treat Fe overload in hereditary hemo-chromatosis and b-thalassemia. Due to the high costs of natural hepcidin for applications of human and un-favorable pharmacologic characteristics, Preza et al. (37), designed minihepcidin derivatives based on the hepcidin mutagenesis and the hepcidin-binding part of ferroportin and computer modelling of their docking. Minihepcidin derivatives showed potent *in vitro* and *in vivo* bioactivity. However, the chemical structure of minihepcidin contains a thiol-free-cysteine group at site 7 for amino acids, this group which is critical for its bioactivity.

Figure 2. Sequence alignment of amino acid of the peptide of LEAP-1/hepcidin, mBD-8, mBD-7, hBD-2 and hBD-1. The cysteine residues forming disulfide bonds are in bold type. The disulfide pattern for the b-defensins is indicated.

However, thiol-group is not preferred in the pharmaceutical field because of the dermatological side effects, in addition to that this group can interact or oxidize depending on conditions reagents, to give a different Cys-derivatives: disulfides, S-alkyl cysteines, sulfones, sulfoxides, cysteic, and cysteine-sulfinic acids (37). Therefore, to reduce this interaction and to maintain the dynamic activity of the mini-hepcidin, Fung et al. (11), have strategically protected the thiol group by activated vinyl thioethers with the keep of their bioactivity.

They used 1,2-double sub-stituted vinylsulfides as an alternative to protection, which can be synthesized from unsaturated alkanes and un-protected free-cysteine which contained the peptide in watery media (Figure 2).

Mostly, all new derivatives (Figure 3) offered high capacity in the low nanomolar domain. Interestingly, the chemical manufacturing of S-substituent was not a clear and specific effect on bioactivity. Nevertheless, the major role was the steric hindrance to compensate. Besides, there are other effects such as the hydrophobicity and the geometry of substituents of the vinyl (11).



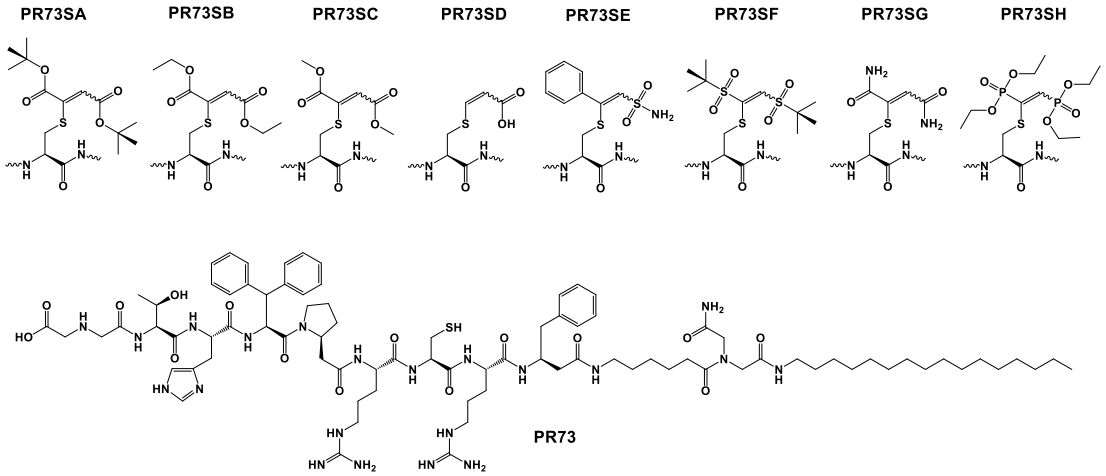


Figure 3. The general structures of the S-derivatized PR 73 analogs (11)

Minihepcidin contains unusual amino acids, including b-homo-amino acids (beta-homo-L-proline (β hPro), beta-homo-L-phenylalanine (β hPhe)) and 3,3'-diphenyl-L-alanine (Dpa).

Unusual amino acids cause a high cost of manufacturing, especially in the large amounts. So, Kristine Chua et al. (6), sought for limiting usages of expensive and unusual amino acids using cyclization of the peptide, the newly cyclic mimetics of the hepcidin have been synthesized by the solid phase method (Figure 4).

The most functional analogs, mHS 26 and mHS 17 (Figure 5) were greatly less expensive for producing than prototypic, parental minihepcidin PR 73, nevertheless they exhibit no *in vivo* potency based on equimolar administration in the mouse model.

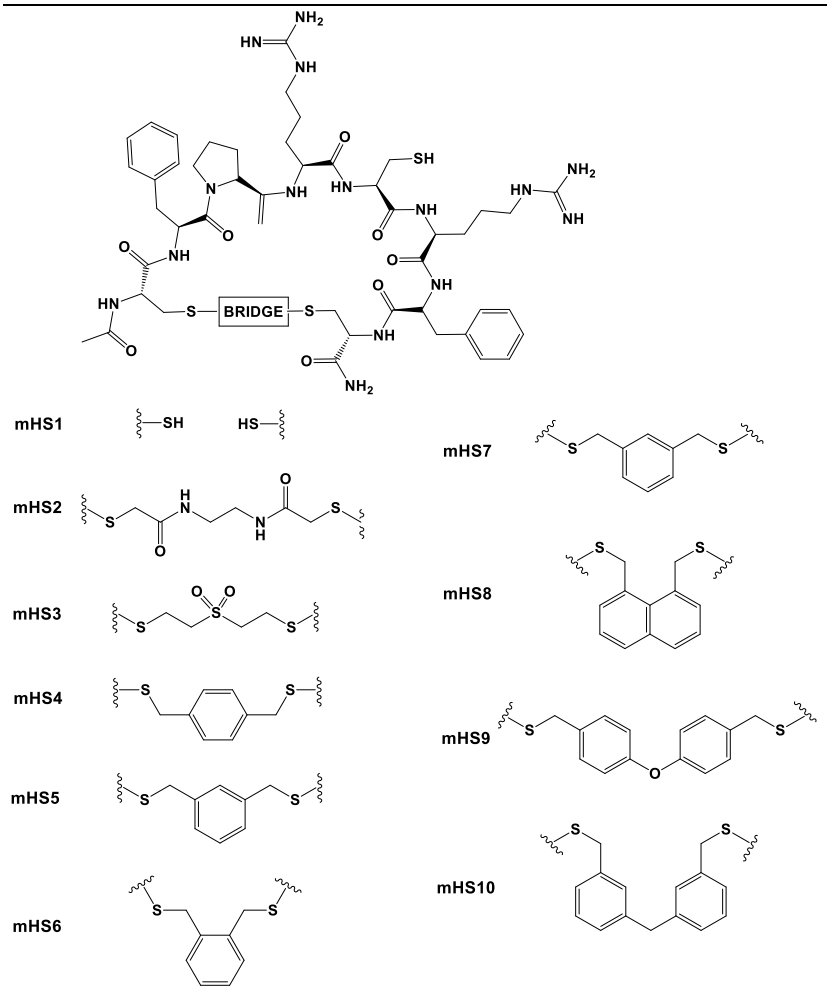


Figure 4. The general structures of the chemosynthesized analogs mHS10–mHS1 (6)

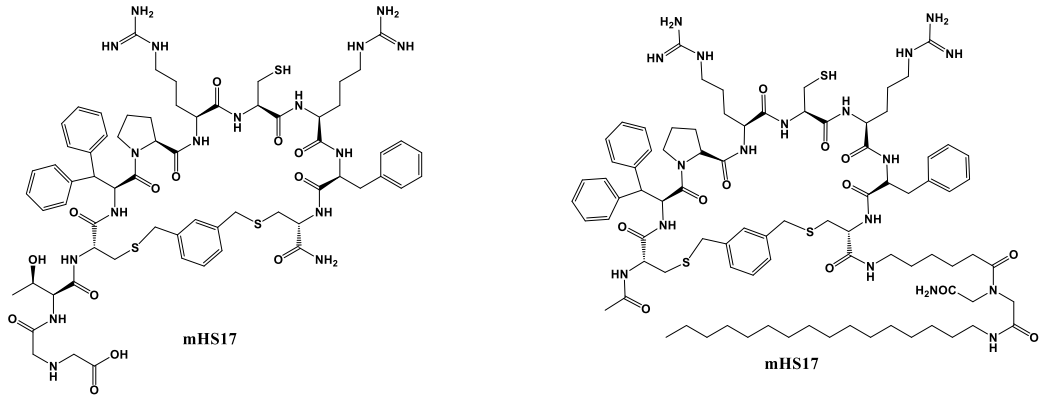


Figure 5. Structures of mHS17 and mHS26.

The function

Hepcidin is one of the regulators of the metabolism of iron. It inhibits transport of iron during binding to the Fe export channel ferroportin which is located on the basolateral surfaces of the gut enterocyte and the plasma membranes of the reticulo-endothelial cells (macrophage). It finally breaks down the transporter proteins in lysosomes. The inhibition processes of ferroportin prevent Fe from being exported and the Fe is sequestered in cells (16,38). By inhibiting ferroportin, hepcidin prevents the enterocyte from allowing Fe into the hepatic portal system, thereby reducing the absorption of dietary Fe. Also, the Fe release from the macrophage is reduced using inhibition of ferroportin.
Partially, increased hepcidin efficacy is responsible for the availability of the reduced Fe shown in anaemia of chronic inflammation like the renal failure (2).

The regulation

Hepcidin encodes using the gene HAMP. It is the hormone that organizes the metabolism of iron. It is the 25-aa peptide produced by the hepatocyte interaction with the ferroportin present in the cellular membrane of the enterocyte, macrophage and hepatocyte (14). Hepcidin regulation is the multi-factorial process including various signals of inhibitory and stimulatory which, in different pathways, control its final transcript (14,22).

The hepcidin was organized using iron of plasma throughout mechanism of feedback which includes extra and intra cellular Fe-sensors coupled to 1 or more signal transduction ways (7). On another hand, the ERFE human gene regulates producing Erythroferrone and inhibits hepcidin (22).

The secretion and synthesis of hepcidin using the liver were controlled using stores of Fe in the macrophage, erythropoiesis, hypoxia and inflammation. The macrophage communicates with hepatocytes for the regulation of the release of hepcidin into blood across 8 various proteins: heriditrary hemo-chromatosis protein, hemojuvelin, BMP 6 (bone morphogenic protein 6), transferrin receptor 2, neogenin, matriptase2, transferrin and receptors of BMP (42). Vit. D showed to reduce the hepcidin, in models of cell looking at the transcription and when given in high doses to volunteers of human. The optimal function of the hepcidin may be predicated based on the adequate presence of vitamin D in the circulation (3).

Chemical mechanisms of the hepcidin

Hepcidin is well known as Fe-regulatory hormone. Mainly, hepcidin causes decreasing in the iron of serum. The hepcidin activity mechanism depended on interactions of hepcidin with the ferroportin. Ferroportin is the only known mammalian cellular iron exporter, which is expressed on surfaces of the reticuloendothelial macrophage, duodenal enterocyte, hepatocyte and cells of the placenta. Hepcidin regulates post-translationally expression of ferroportin, binds to the ferroportin and causes its internalization and degradation in the endolysosome, what in turn blocks the transport of iron via ferroportin. When stores of iron are high or adequate, increased hepcidin expression is inhibiting the absorption of the intestinal iron, release of the recycled iron from the macrophage and its transport across the placenta. On the other hand, when stores of iron are low, the production of hepcidin is suppressed. By modulating hepcidin expression, organisms can control the iron level in plasma and maintain Fe metabolism homeostasis (30) as in Figure 6.

In the absence of the controlled excretion mechanisms, regulation of levels of body Fe generally takes place through its absorption using duodenal epithelia. The process of absorption of intestinal iron comprises 3 successive steps: the iron uptake from the intestinal lumen; the intracellular phase, in which Fe binds to the cytosolic components; and the transfer step, in which Fe exits the cells into the plasma of blood (32).

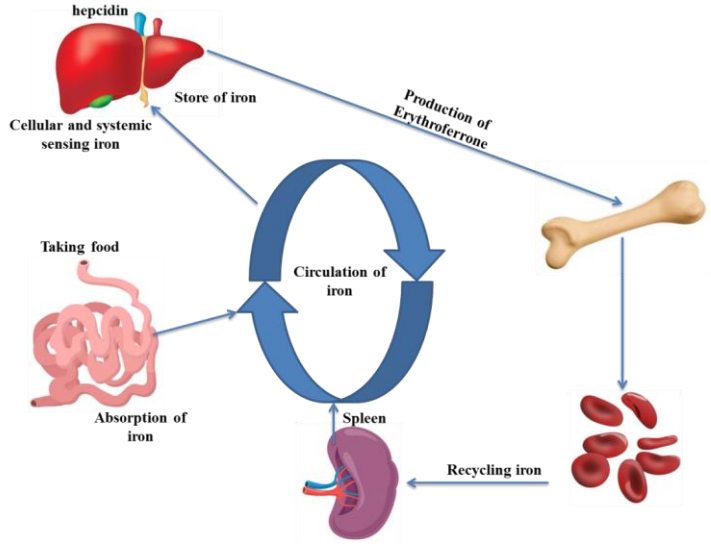


Figure 6. Regulating and circulating iron in the human body

Antimicrobial activity of Hepcidin

Hepcidin has antibacterial and antifungal activities. It inhibits the growth of positive and negative bacteria like *Staphylococcus aureus*, *Aeromonas hydrophila* and *Escherichia coli* (23). Hepcidin significantly exhibited the growth of *Aeromonas sobria* (17), *E. coli* (17,19,23,29), *Bacillus subtilis* (17), *S. aureus* (17,23,28), *Pseudomonas aeruginosa* (28), *Acinetobacter baumanni*, *Stenotrophomonas maltophilia*, *Klebsiella pneumoniae*, *Staphylococcus epidermidis*, *Enterococcus faecium* (28), *Edwardsiella tarda* (29), *Aeromonas hydrophila* (23,29,39), and *Streptococcus iniae* (39). Also, hepcidin showed antifungal activity against *Aspergillus fumigatus*, *Aspergillus niger* and showed anticandidal activity against *Candida albicans* (36), and *Candida glabrata* (15).

CONCLUSION

Hepcidin (small bactericidal peptide) is considered a vital regulator of the iron entry in the blood of mammals. Hepcidin, a 25 amino acids long peptide hormone, has antimicrobial activity, especially in urine. Also, many remarkable results exhibited antibacterial, antifungal and anti-candidal activity against multidrug resistance pathogens, *in vitro*. The central of its formation is cells of the liver (hepatocytes). The expression of Hepcidin is low when iron stores of the human body are insufficient.

Conflict of interest

No conflict of interest was declared by the authors.

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