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The Biological Role of Haptoglobin and Behaviour of This Protein in Different Diseases, with Special Attention Paid to Brain Stroke

Biologiczna rola haptoglobiny oraz zachowanie się tego białka w różnych schorzeniach, ze szczególnym uwzględnieniem udaru mózgu

Haptoglobin (Hp) is an alpha 2 glycoprotein, the presence of which was determined in blood serum in 1940 by Polonovski and Jayle. Smithies showed genetically conditioned polymorphism of haptoglobin (4,16).

Molecular heterogeneity of haptoglobin is demonstrated by three main phenotypes: Hp 1—1, Hp 2—2, Hp 2—1. Haptoglobin is a glycoprotein with tetrametric structure. Haptoglobin 1—1 is composed of two alpha (light) chains with 9,000 molecular mass including 83 aminoacids and two beta (heavy) chains with 40,000 molecular mass including 245 aminoacids. Alpha chains are connected with each other by two sulfurous bonds which also connect alpha chains with beta chains (3, 4).

Saccharides compose about 20% of haptoglobin molecule, 5% of which is terminally placed sialic acid. It has a terminal place in two three-antennal and two two-antennal oligosaccharide chains (3, 10).

Beta chain is identical in three haptoglobin types, whereas alpha chains are the source of microheterogeneity. In haptoglobin 2—2 $alpha_1$ chain is found while in haptoglobin 2—1 beside $alpha_2$ chains $alpha_1$ chains are found too (1).

Regulation of haptoglobin gene expression takes place on three levels: the one connected with ontogenesis control which is responsible for the lack or minimal expression in foetus liver; control of tissue specificity connected with selectivity of gene expression in hepatocyte; modulation of expression during acute phase reaction (5).

Regulation of reversible connection on hypothalamic-pituitary-suprarenal gland axis is made by three modulating factors in general working synergistically, which are cytokines, glycocorticoids and catecholamines (10).

Haptoglobin synthesis in liver takes place after a stimulation of hepatocytes by cytokines produced by macrophages and other cells in the place of tissue damage. Macrophages create numerous proteins and biologically active peptides to which belong: interleukin 1 and 6, tumour necrotic factor (TNF), hepatocyte stimulating factor (HSF), interferon (IFN) and others. Comediators are prostaglandins, histamine, serotonin. Interleukin 6 (IL-6), interleukin 1 (IL-1) and TNF are the main regulators of haptoglobin synthesis. Interleukin 6 works on transcription level, causing an increase of m RNA haptoglobin and it influences its glycation (5,10).

Haptoglobin is synthetised as one polypeptidal chain, including sequences of alpha and beta subunits cotranslatingly glycosyled in beta region and diffused into alpha and beta subunits connected by twosulfurous bonds. The last stage is the creation of tetramers (Hp-1) and polymers (Hp 2—2 and Hp 2—1) (3).

Catabolism of haptoglobin takes place in the liver. After diffusion of sialic acid it is removed from circulation because it joins with specific receptors (lectines) of hepatocytes (3).

The biological role of haptoglobin is not precisely defined all the more so as human being can exist without this protein in blood, and not showing morbid symptoms (5). Biological and immunological characteristics of haptoglobin depend on changs in its molecule structure (3). Tissue necrosis, occurring also in brain stroke, leads to local freeing of lysosomal hydrolases digesting and removing necrotic concretions. Excessive and uncontrolled activity of these proteinases may lead to secondary damages in tissues. Haptoglobin competisively breaks lysosomal cysteinal proteinases: cathepsin C and cathepsin B and L. It was stated that breaking of cathepsin B by haptoglobin is reversible in the presence of monospecific antihaptoglobinal antibodies (4, 9, 10).

It was shown that haptoglobin is a nature antagonist of activating immunological system receptors. Samak and coworkers described breaking of blastogenic response of lymphocytes in human blood

stimulated by phytohemagglutinin in the presence of high concentration of haptoglobins and breaking of lymphocytes B mitogenesis (14). Haptoglobin blocks neutrophils response and restrains the production of peroxides, and also modulates macrophages function (3, 4, 5, 10). The outcome of haptoglobin activity is the suppression of immunological reaction (14).

Leucocytes, macrophages and other cells gathering in the place of the damaged tissue, are a source of free radicals and peroxide ions, prostaglandins and other mediators. Shim suggested that human haptoglobin may regulate prostaglandin synthesis by restraining influence on prostaglandin synthesis activity. The presence of endogenic inhibitor of prostaglandin synthesis in blood serum was stated. Later experiments showed that its activity is linked with haptoglobins which pointed to the presence of a natural mechanism of controlling prostaglandin synthesis. At the same time it was showed that in *in vitro* system, haptoglobin may decrease creating of prostaglandins by limiting hem group accessibility, which is demanded to a full activity of the enzyme. Haptoglobin and hemoglobin complex may play a significant role in restraining of the creation of hydroxylic radicals by hemoglobin in inflammation areas (3, 10).

Haptoglobin bounds hemoglobin irreversibly. The created compound shows peroxidase activity. It was showed that 1,3 g of haptoglobin bounds 1 g hemoglobin. The presence of haptoglobin and hemoglobin compound prevents the loss of iron. This compound undergoes the endocythosis in the cells of reticuloendothelial system of the liver, whereas iron remains to be used in further changes. This is a very important function of haptoglobin, because it not only lets iron stay in the system but also because free hemoglobin and its iron aids the increase of bacteria (3, 4, 10, 16).

It was suggested that haptoglobin has an ability to restrain virus hemagglutination, and it also may play a role of the natural bacteriostatic agglutinating streptococcus with antigen T_4 and bounding Actinomyces pyogenes (4, 5, 6).

Haptoglobin occurs in many human system fluids: blood serum, urine, cerebro-spinal fluid, amniotic fluid, saliva, joint fluid, exudate and transudate fluids in different concentration depending on tissue spe-

cificity and on the physiopathological state of the system. It is not present in 80—90% of infants up to four months old which results from foetus erythrocyte hemolysis and immaturity of parenchymal cells and reticulo--endothelial system of the foetus liver to biosynthetize and degrade haptoglobin. In adults ahaptoglobulinemia and hypohaptoglobulinemia may occur (4, 10).

Haptoglobin is a protein which undergoes two pathophysiological phenomena: the rising level in acute phase and the falling one in damaging liver parenchyma as a result of restraining biosynthesis or secretion by hepatocytes or the secondary fall of the level as a result of hemolysis and bounding haptoglobin by hemoglobin (4).

According to Koj's classification haptoglobin belongs to strong proteins of acute phase, the concentration of which in serum increases 2—5 times. However, if absolute changes of concentration should be taken into consideration, haptoglobin occupies the main position among acute phase proteins (10).

The increase of haptoglobin level was observed in numerous diseases: rheumatic, meningitis, heart muscle infarct, in neoplasmatic diseases, diabetes, infectious-inflammatory diseases, and brain strokes (4, 8, 12, 15, 16, 17, 18).

Two kinds of changes were observed in leukemias; allergy and chronic alcoholism, whereas the fall of the level was noticed in hemolytic and megaloblastic anaemia and haemophilia A, inflammatory liver states and liver cirrhosis (4).

Serial estimation of haptoglobin level may be useful in differential diagnostics of malignant and benign tumours, haemolytical and non-haemolytical anaemia, coronary disease and heart muscle infarct (4, 12).

The examination of haptoglobin level carried out in blood of patients with brain stroke showed a statistically essential increase of this protein level (8, 12, 16).

Strugalska did not show any greater differences in the haptoglobin level depending on stroke mechanism. She noticed an increase of this parameter from 2nd — 3rd day of the illness till around the 14th day, and then lowering of haptoglobin level to normal. Strugalska, while analysing autopsical material, did not show any correlation between the haptoglobin level in blood and the size of the infarct focus (16).

Iłżecka and Ponikowski observed a statistically valid increase of haptoglobin level till the 7th day of brain stroke and a gradual normalisation of its level during the following two weeks (8, 12).

The correlation between haptoglobin level in blood serum in patients with brain stroke and the size of infarct focus in computer tomography test was found. Hornig's works show that great infarct foci causing clinically heavier disease process make greater damage in blood-brain barrier (7). That is where the differences between freeing mediators of acute phase reaction may come from; it causes different haptoglobin activity in blood of patients with more and less active clinical process of brain ischaemic stroke (8). However, a comparative analysis of the protein behaviour in blood in patients with more and less active process of brain ischaemic stroke did not show any statistically crucial differences.

A comparative analysis of haptoglobin levels in blood of patients depending on the kind of brain stroke, showed a higher content of this parameter in blood in patients with cerebral haemorrhage in comparison with content of this protein in blood of patients with brain ischaemic stroke. This difference was statistically important (8).

Transient ischaemia of the brain causes an increase of haptoglobin level in patients blood. This level persists on the third and second day of the illness. Brain ischaemia may cause damage of neurons in the selectively sensitive brain area, which can evoke only active reaction of acute phase in blood.

Koj and other authors connect the comparatively low level of haptoglobin on the first day of illness with the fact that haptoglobin is a protein which in the early stage of acute phase may show transient fall because of increased vascular penetrability and increased catabolism (10).

The difference in the haptoglobin level, which changes depending on the clinical shape of acute vascular brain damage, is connected with different speed of this protein synthesis in liver, whereas disturbances in mechanism of blood-brain barrier or freeing haptoglobin from damaged brain tissue play a minor role.

In the literature the role of indicating haptoglobin level as a protein of acute phase in recognising different diseases, in evaluating seriousness of clinical condition of patients, in monitoring therapy process is stressed (4, 11).

The aim of the examination of using haptoglobin in clinical medicine was estimation of interdependence between haptoglobin phenotype and susceptibility to certain diseases. These investigations, started by Peacocke and continued by others, taking into consideration controversy of the results, did not yet lead to explicit effects both cognitively and practically (2).

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STRESZCZENIE

Przedstawiono biologiczną rolę białka osocza — haptoglobiny — w ustroju człowieka.

Z piśmiennictwa wynika, że monitorowanie poziomu haptoglobiny we krwi chorych może być pomocne w medycynie klinicznej w różnicowaniu jednostek chorobowych, w ocenie skuteczności terapii oraz w rokowaniu.

Zwrócono uwagę na zachowanie się haptoglobiny we krwi pacjentów z różnymi schorzeniami, ze szczególnym uwzględnieniem ostrego naczyniowego uszkodzenia mózgu.