ANNALES
UNIVERSITATIS MARIAE CURIE-SKŁODOWSKA
LUBLIN — POLONIA
VOL. LI, 14 SECTIO D 1996

Katedra i Klinika Neurologii Akademii Medycznej w Lublinie
Kierownik: prof. dr hab. Wiesław Kawiak

JOANNA IŁŻECKA

The Protective Role of Ceruloplasmin Against the Activity of Free Radicals in Brain Ischaemia

Ochronna rola ceruloplazminy przed działaniem wolnych rodników w niedokrwieniu mózgu

Free radicals are atoms, groups of atoms or particles having on their last orbital at least one unpaired electron. This feature decides about their great chemical reactivity and lability (12, 16).

To potentially toxic oxygen radicals belong: peroxidal anion radical, hydroxidal radical, hydrogen peroxide, hydroxylic radical, peroxidal lipid radical, singletal oxygen (12).

The presence of free radicals in biological systems may play a role in etiopathogenesis of different illnesses. Overactivity of these compounds causes damage of tissues and bodily organs (3, 16, 18).

The central nervous system is especially susceptible to ischaemia and anoxia. Ischemia causes biochemical changes in the brain characterized by depolarization of neurons' membranes. As the outcome of ischaemiac depolarization potassium ions come out of the cells and sodium and calcium ions come into the cells. Neurotransmitters, stimulating amino-acids including, are released in a toxical quantity (7, 13). An important generator of free radicals is xanthinal oxidase. Tissue ischaemia and following reperfusion causes the conversion of dehydrogenase into oxydase. In anoxiac conditions oxidative phosphorylation has small efficiency, which causes the catabolism of excess adenosine into hipoxanthine. It is considered that the damage of the tissue is caused by repeated restoring of circulation (reperfusion) which causes greater oxygen saturation. Then overproduction of free radicals is created in the xanthinal oxidase system (1, 3, 6).

Free radicals generated in reperfusion cause lipid peroxidation and hyaluronic acid depolymerization, leading to deffects of vessel membranes in consequence of the degradation of its components (3, 109).

Ischaemia causing increase of the intracellular cencentration of calcium ions, activates A_2 phospholipase which releases fatty acids, among others arachidic acid. This compound occurs in the brain areas which are especially susceptible to ischaemia.

The influence of lipooxygenases and cyclooxygenases on arachidic acid causes the creation of prostanoids eliciting vessel spasm and free radicals secondarily damaging the brain tissue (1, 7, 17).

Arachidic acid together with free radicals provokes brain swelling through the influence on blood-brain barrier causing an increased penetrability. Swelling of the brain tissue comes out of hampering ATP-ase Na-K by arachidic acid (7).

The extent of the brain tissue damage depends among others on the degree, placing and duration of ischaemia and metabolic constitution of brain tissue before the ischaemia episode.

Short-lived ischaemia may lead to the damage of the most susceptible neurons. After one hour of focal ischaemia brain stroke follows. It is characterized by the death of neurons, glia and other supporting cells in the limits of the affected area of vessels (13).

Human organism using oxygen in its metabolism has a protective system which protects the cell against destructive activity of free radicals, called antioxidizing system (3, 12, 18).

Cellar regulators of the concentration of toxic oxygen forms are enzymes: catalase, glutathionic peroxidase and peroxide dismutase. Vitamin E belongs to tissue antioxidants preventing the activity of free radicals. Cysteine and cystamine may neutralize activity of free radicals by adding an electron coming from their sulphydryl group. Vitamin C has also antioxidizing effect if given in large doses (12).

Ceruloplasmin is an extracellular antioxidant. It belongs to the alpha 2 globulin fraction (2, 3, 18).

Ceruloplasmin molecular mass is about 132,000 daltons. It owns one polpeptide chain composed of 1,046 amino acids. In a single polypeptide chain there are three literal carbohydrate chains two-or three-antennar.

Ceruloplasmin synthesis occurs in parenchymal cells of the liver on ribosomes of andoplasmatic reticule as a result of affecting its mRNA. Ceruloplasmin synthesis induction occurs under the influence of interleukine-1 and cachektine. Ceruloplasmin is synthetised as a precursor with molecule mass around 80,000 daltons and then changed into a final form.

The activation and synthesis of ceruloplasmin gene is influenced by glycocorticosteroids, cyclical AMP, copper ions, estrogens, thyroid hormones, somatotropin (2, 4).

Polymorphic instability of ceruloplasmin is conditioned by the presence of three allels of this protein. Different genetic variants are probably responsible for the differences in oxidizing activity of ceruloplasmin.

Ceruloplasmin plays a significant role in metabolism of copper and iron ions, activation of aromatic amines oxidase, it has an antioxidizing and probably immunomodulative role. Ceruloplasmin functions as a central molecular focus of copper and iron ions metabolism. As the main protein transporter of copper it delivers this metal to tissue enzymes like cytochromic oxidase. It owes the influence of oxygen metabolisn to the presence of copper atoms in its molecule. Ceruloplasmin brakes a series of enzymatic reactions with the participation of peroxide ions through the dismutation reaction and removes hydroxyl radicals and free oxygen through mechanisms not yet explained (2, 4, 10, 12, 18).

To ceruloplasmin is ascribed a function of an inhibitor of lipids peroxidation, because it hampers the oxidizing of unsaturated aliphatic acid of lipids as a result of enzymatic oxidizing bivalent iron into a trivalent one (18).

Ceruloplasmin controls releasing of iron from liver cells, changing it and building it into a transferin molecule. Iron ions bound to transferin may be transported into tissues. For maximal releasing of iron ions 5% of proper concentration of ceruloplasmin is sufficient.

Oxidizing activity of ceruloplasmin concerns biogenic amines, adrenaline, serotonine, noradrenaline, ascorbinians and some sulphydryl compounds (3, 18).

Tissue damage, brain tissue including, may follow when antioxidizing system becomes insufficient as a result of excessive releasing of free

radicals or in pathological conditions connected with disturbances in functioning (12).

Regulatory-protective function of ceruloplasmin connected with removal of free radicals is showed by an increased synthesis of this protein in liver and its increased concentration in serum. Ceruloplasmin concentration in blood serum increases by 20—60% in different diseases. (18).

The increase of ceruloplasmin level was showed in brain strokes, heart muscle infarct, neoplasmatic diseases, infectious-focal processes (2, 5, 9, 11, 14, 15).

The increased level of ceruloplasmin in serum may be a reflection of neoplasmatic process in which the relapse in illness is accompanied by the increase of this protein level in blood serum (5, 9).

In cerebral strokes the highest levels of ceruloplasmin were noticed in blood of patients with cerebral haemorrhage, lower level of this protein in blood of patients with cerebral ischaemic stroke, and the lowest level of ceruloplasmin in patients with acute transient brain ischaemia. Levels of the examined protein in serum of these patients correlated with the degree of brain tissue damage (8).

The systematic fall of ceruloplasmin level in all clinical cases of brain damage in the following days of the illness was shown. The increased dynamics of ceruloplasmin level changes correlated with favourable evolution of the illness (8, 15).

REFERENCES

1. Armstead W. M. et al.: Postischemic generation of superoxide anion by newborn pig brain. Am. J. Physiol., 401, 255, 1988.
2. Błasińska M., Wilczyński J.: Aktywność ceruloplazminy w niektórych ostrych i przewlekłych stanach zapalnych u ludzi. Wiad. Lek., 971, 11, 1980.
3. Broadley C., Hoover R. L.: Ceruloplasmin reduces the adhesion and scavenges superoxide during the interaction of activated polymorphonuclear leukocytes with endothelial cells. Am. J. Pathol., 647, 135, 1989.
4. Broniek S., Grzybowski G.: Metabolizm ceruloplazminy i jej biologiczna rola w utrzymywaniu homeostazy ustroju. Post. Biol. Kom., 23, 15, 1988.
5. Casamassima A. et al.: Serum levels of ceruloplasmin, properdin factor B and copper in lymphoma patients. Int. J. Biol. Markers., 183, 6, 1991.

6. Chambers D. et al.: Xanthine oxidase as a source of free radical damage in myocardial ischemia. J. Mol. Cell. Cardiol., 313, 34, 1982.
7. Farbiszewski R.: Udział wolnych rodników w mechanizmie uszkodzenia tkanki mózgowej. Neur. Neurochir. Pol., 729, 27, 1993.
8. Iłżecka J.: Zachowanie się niektórych czynników ostrej fazy — kwasu sialowego (N-acetyloneuraminowego) całkowitego, kwasu sialowego (N-acetyloneuraminowego) związanego z lipidami, haptoglobiny, ceruloplazminy — we krwi chorych z ostrym naczyniowym uszkodzeniem mózgu w najwcześniejszym okresie choroby. Praca doktorska, AM Lublin 1994.
9. Manjula S. et al.: Elevation of serum ceruloplasmin levels in brain tumours. Acta. Neurol. Scand., 156, 86, 1992.
10. Mc Cord J.: Oxygenderived free radicals in postischemic tissue injury. New. Engl. J. Med., 159, 3, 1985.
11. Natesha R. K. et al.: A prognostic role for ceruloplasmin in the diagnosis of indolent and recurrent inflammation. J. Natl. Med. Assoc., 781, 84, 1992.
12. Pawłowicz Z. et al.: Wolne rodniki i ich antyoksydanty. Wiad. Lek., 884, 17, 1990.
13. Pulsinelli W.: Pathophysiology of acute ischemic stroke. The Lancet, 533, 339, 1992.
14. Reunanen A. et al.: Serum ceruloplasmin level and the risk of myocardial infarction and stroke. Am. J. Epidemiol., 1082, 136, 1992.
15. Suciu A. et al.: Study of serum ceruloplasmin of the copper zinc ratio in cardiovascular diseases. Med. Interne., 193, 30, 1992.
16. Waniek A. et al.: Rola wolnych rodników w patologii człowieka. Pol. Tyg. Lek., 195, 10, 1990.
17. Wieloch T., Siesjo B. K.: Ischemic brain injury: the importance of calcium, lipolytic activities and fatty acids. Pathol. Biol., 269, 30, 1982.
18. Winyard P., Lunec J.: Action of free radical generating system upon the biological and immunological properties of ceruloplasmin. Int. J. Biochem., 1273, 12, 1984.

Otrz. 1996.04.16

STRESZCZENIE

Przedstawiono rolę wolnych rodników w patomechanizmie uszkodzenia tkanki mózgowej oraz system antyoksydacyjny, do którego należy ceruloplazmina.

Z piśmiennictwa wynika, że w przebiegu różnych schorzeń, również naczyniowych uszkodzeń mózgu, dochodzi do wzrostu tego białka w surowicy krwi chorych.