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Editorial

Effects of Free Hemoglobin in Human Pathologies

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Bleedings and hemolysis are parts of human diseases. For many years free hemoglobin derived from red blood cells were not considered to play any role in pathophysiology of human diseases, since hemoglobin was supposed to be an innocent pathological bystander, and at the same time a well-known catabolic system is available taking care of hemoglobin at bleeding sites and in the blood. Although surgeons are extremely careful during operation aiming to avoid blood containing environment knowing that the remaining blood may cause complications, such as necrosis, inflammation, prolonged wound healing. Today neurologists are aware of the vasospastic phenomenon in subarachnoideal hemorrhage, where free hemoglobin can lead to vasospasm through its ability to behave as a sink for nitric oxide, a strong vasodilator gas, in the central nervous system. In rhabdomyolysis, hemoglobin and another hemeprotein, myoglobin, can become free, in other words, they escape form their normal, intracellular environment [1-3]. These hemeproteins act together on kidneys resulting in renal failure and death. In premature newborns, suffering from retinopathy of prematurity, retinal bleeding is a risk factor of neonatal vision loss. Although certain sports are associated to pathologies of central nervous system, i.e. Parkinson's disease in boxing, early dementia in brain injuries, there is no scientific data between free hemoglobin and brain diseases. There are enormous data in the literature about brain diseases and iron, especially in those papers what give information about the interaction of iron and free radicals. The kern-icterus is the worst neuropathology in newborns suffering from severe intravascular hemolysis. The basic cause of this injury is thought to be bilirubin toxicity of basal ganglia. The treatment of the severe neonatal hyperbilirubinemia is exchange blood transfusion and bilirubin modification, i.e. blue light treatment leading to bilirubin isomerization. The role of free hemoglobin in this neonatal disease also has not been considered yet.

The aim of our research group was to study all of the players of hemolytic and bleeding processes in human diseases from the newborn age till the adulthood. This systematic work contained cell culture and animal models, human genetic disorders and clinical studies. Here we summarize our achievement, and raise open questions for future studies.

We was the first in the literature proving the role of free hemoglobin and heme, released from hemoglobin in vascular endothelial cell injury [4]. Free heme tremendously was able to increase endothelial cell sensitivity to reactive oxygen species resulting in cell death through lipid peroxidation mechanism. Since oxidized low density lipoprotein and iron can be found in atherosclerotic vessels, we tested whether free heme may oxidize LDL. Heme was as active in LDL oxidation as it was in endothelial cell injury, more over modified LDL was toxic to endothelial cells [5]. During heme effect iron is released from heme and the remaining porphyrin ring also degrades. This is the reason why heme cannot be found in vascular walls, so iron is its footprints meaning the importance of heme in vascular pathologies with elevated tissue iron concentration. Based on our results a lot of studies has been started in the literature. We opened the research field of heme toxicity in human diseases. The importance of free hemoglobin and heme toxicity is underlined by the existence of protective proteins in the blood. Haptoglobin binds free hemoglobin, hemopexin links to free heme in a way not only carrying them to the liver but preventing them to deliver free heme to lipid domains of cells and lipoproteins. In this way, these proteins are the first protective lines against heme toxicity. Next, we ask the question whether there is another protective mechanism against heme toxicity. Heme oxygenase metabolizes heme to biliverdin, iron and carbon monoxide. At the same time intracellular ferritin is synthesized, especially H-ferritin having. H-ferritin possesses ferroxidase activity and iron soring capability [6]. After 16 - 20 hours of heme effect, these proteins are induced

inside the cells tremendously, and provide effective protection against any type of reactive oxygen species. Our discovery started a new field in the antioxidant research, i.e. a new, natural, intracellular, inducible antioxidant system, we called it heme oxygenase-ferritin system.

In summery we established the acute- and chronic heme effect theory, which is the following. Acute heme effect is toxic through its catalytic effect on free radical reactions and iron releasing capability. Chronic heme effect is protective through its capability to induce heme oxygenase and ferritin. Heme oxygenase provides its protection by decreasing the toxic cell and tissue heme content, produces antioxidant bilirubin by the help of biliverdin reductase, and carbon dioxide. CO may also have protective roles, for example locking heme in hemoglobin, in this way preventing production of free heme. Ferritin, mainly H-ferritin takes care if iron coming from heme, since oxidation of iron inhibits it catalytic activity in Fenton reaction, and ferric iron atoms are stored in the ferritin core.

Previously, before our research, ferritin was considered to be a prooxidant protein, since ferritin was found in those tissue locations, where metabolites of reactive oxygen species were also found. As a result of our research, the surmise of nature of ferritin has been changed, today it is a protective protein, a preventive reaction of organisms against the iron driven free radical toxicity, especially if the source of iron is heme.

The existence of heme oxygenase-ferritin system can be found in animal models, for example in rhabdomyolysis, lung injury, heart transplantation, cerebral malaria showing by us [7]. The importance of the whole system was presented by the help of heme oxygenase deficient children. They suffer multiorgan vascular disorders resembling atherosclerosis with inflammatory characteristics.

Using cell culture technics with cells derived from central nervous system, several studies prove the existence of the protective heme oxygenase-ferritin system in the brain. But other studies presents opposite effects in other brain models. One can hypothesize that brain is different from other organs in respect of the role of hemoglobin-heme-heme oxygenase-ferritin system. It is time to dissect this new phenomenon in different brain areas and cells. That is why the value of our early observational study is significant shoving the protective effect of an antioxidant and metal chelating drug, d-penicillamine on retinopathy of prematurity [8]. Although the pathophysiology of this eye disease is vascular type, but the retina is part of the brain, and may provide information about what is going on in brain pathology.

Much more work has to be done to understand the relationship between the hemoglobin-heme-heme oxygenase-ferritin system and brain pathologies in a more detailed way. Patients are waiting new therapeutic and prophylactic tools, and our discoveries may help in inventing original and effective interventions.

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