

Brain blood barrier defects and ferric-iron brain accumulation as cause of gradually neurodegenerative brain disease

Lucijan Mohorovic^{1*}, Anna M. Lavezzi², Sanja Stifter³, Vladimir Micovic¹ and Eris Materljan⁴

¹Department of Environmental Medicine, University of Rijeka School of Medicine, Rijeka, Croatia

²"Lino Rossi" Research Center, Department of Biomedical, Surgical, and Dental Science, University of Milan, Milan, Italy

³Department of Pathology, University of Rijeka School of Medicine, Rijeka, Croatia

⁴Department of Family Medicine, University of Rijeka School of Medicine, Rijeka, Croatia

Abstract

As a main aim we want to focus on the sources of oxidants as key factors in understanding the role oxidants play in the pathogenesis of brain vascular endothelial dysfunction. The question remains whether iron inversion and subsequent radical formation is a primary or secondary event in neurodegenerative disease.

Recent research suggests that iron inversion is an initial cause of neuronal cell death and axonal degeneration. Methemoglobin and its catabolic products provoke adverse effects in vascular endothelium dysfunction, reduced regenerative capacity and an increased rate of endothelial cell apoptosis.

The main difference between hemoglobin and methemoglobin heme oxygenation is that the final hemoglobin degradation products are bilirubin-biliverdin, CO and ferrous (Fe²⁺) iron, but the final methemoglobin catabolism products are bilirubin-biliverdin, CO and ferric (Fe³⁺) iron, which in a methemoglobinemia pathological condition have an important role, which has a redox-active and cytotoxic property, and as a valuable biomarker.

Introduction

The objective is to focus on methemoglobin as a biomarker which has an important role in the detection of the adverse effects of oxidative stress, the misbalanced production of ROS (reactive oxygen species), RNS (reactive nitrogen species) and RSS (reactive sulfur species). According to our hypothesis, for people who continuously inhale environmental toxins in fuel burning products, methemoglobin as a product of hemoglobin oxidation takes on an important role, causing increased systemic oxidative stress of vital organs.

Strong exogenous oxidants such as NO_x (nitrogen oxides: NO and NO₂) reversibly oxidize oxyhemoglobin (Fe²⁺) to methemoglobin (Fe³⁺), and irreversible methemoglobinemia can arise because of the disruption of the oxidant/antioxidant balance, supported by the synergic SO₂ metabolites degradation of antioxidant thiols. The formation of methemoglobin-ferric iron (Fe³⁺) from hemoglobin-ferrous iron (Fe²⁺) leads to the destruction of erythrocytes, so that free hemoglobin from hemolysis can be directly cytotoxic and can alter the state of endothelial cells and cause endothelial dysfunction. From methemoglobin and heme catabolism, cytotoxic redox-active ferric iron is released into the bloodstream, which contributes to endothelial injury and the development of neurovascular diseases.

Results

Our results, obtained in a large number of cases [1-3,6-8,16-20] show the consequences of maternal-fetal methemoglobinemia caused by environmental oxidants, causing oxyhemoglobin and methemoglobin hemolysis, hyperbilirubinemia and toxic brain damage, and highlight

the role of methemoglobin catabolism as a source of ferric (Fe(III)) form concentrated in various brain regions.

The role of methemoglobin on structural and functional changes in the vascular endothelium

Methemoglobin and hemolysis both occur as a result of oxidative stress, but the prevalent difference between them is that methemoglobin is a reversible phenomenon (oxidant-antioxidant balance) whereas hemolysis, which occurs as a result of oxidative stress on the erythrocyte membrane, is an irreversible event. Methemoglobinemia can additionally exacerbate existing anemia, stimulating hypoxia that may also be dangerous.

Our prospective study of methemoglobin in pregnancy showed a significant rise in the level of methemoglobin >1.5 g/L ($r = 0.72$, $p < 0.01$) in the air-polluted exposure period, which can be explained by an oxidant-antioxidant imbalance, resulting in methemoglobinemia [1]. The methemoglobinemia and stillbirth recorded throughout the exposure period are significantly higher than those recorded in the control period ($p = 0.0205$) and the frequencies of reproductive loss were significantly lower in the *control* than in the *exposure* period ($p <$

Correspondence to: Lucijan Mohorović, MD, PhD, Department of Environmental Medicine, University of Rijeka, School of Medicine, Croatia, E-mail: lucijan.mohorovic@pu.t-com.hr

Key words: biomarkers methemoglobin catabolism, brain blood barrier, brain ferric iron accumulation, neurodegenerative diseases

Received: June 22, 2017; **Accepted:** July 28, 2017; **Published:** July 31, 2017

0.05) [2]. In healthy women, methemoglobin comprises less than 1% of haemoglobin, but this ratio rises in pathophysiological conditions when red blood cells are affected by genetic, xenobiotic, pharmaceutical, idiopathic or toxic agents from food and chemical compounds from the environment [3,4].

As I have found no evidence of the consequences of maternal methemoglobinemia on the fetus, the second objective is to focus on methemoglobin as an early biomarker of the oxidative stress effects of environmental toxins, which put pregnancy at risk and may later impair the health of newborns, children and adolescents. High concentrations of methemoglobin and its catabolites affect the function of the kidney, the brain, and other vital organs, and are manifested as maternal preeclampsia and/or fetal preeclampsia [5]. The increase of maternal methemoglobin could be a useful biomarker to determine when the health of pregnant women is threatened by toxic substances in the environment. The conversion of haemoglobin to methemoglobin (a ferrous to ferric state) leads to haemolysis [6], and the consequences thereof.

Discussion

In methemoglobinemia pathological conditions, methemoglobin catabolises into heme, and the activity of heme-oxygenase leads to products such as bilirubin-biliverdin, carbon monoxide, and Fe (III) with paramagnetic and toxic properties. Acting as oxidants, methemoglobin and heme affect the function of the capillary endothelium of the blood-brain barrier, facilitating the passage to the brain parenchyma of harmful substances such as methemoglobin and heme, and/ or the deposition of toxic ferric (III) iron in the brain.

It is well known that ferrimethemoglobin (III) releases heme in the endothelial cells, inducing increased hem-oxygenase activity and ferritin production. In fetal blood, nitric oxide and superoxide form peroxynitrites (ONOO-), which converts oxyhaemoglobin into methemoglobin, and the methemoglobin-released heme induces endothelial cytolysis [7-11].

Iron is essential for normal cell function, but it also generates toxic ROS that adversely affects vascular endothelium and the blood-brain barrier [12]. Astrocytes distribute iron in the brain and possess transporters for transferrin-bound, haemin-bound, and non- transferrin-bound iron [13]. In the brain, non-heme-bound iron is mostly found in ferritin. Nowadays, non-heme-bound Fe (III) is quantified using magnetic resonance imaging (MRI), thanks to its paramagnetic properties [14]. It is believed that most non-heme-bound iron is deposited in the form of ferritin, haemosiderin, or methemoglobin catabolic products [15], whereas transferrin-bound iron concentration is always low and cannot be detected by MRI.

Conclusion

Vascular endothelial cells are direct targets for free hemoglobin and for its oxidative derivative methemoglobin which readily releases heme, an abundant source of redox-active ferric iron which impacts on brain vascular endothelial dysfunction and apoptosis performing ferric-iron brain accumulation on the endothelium and cause brain capillary defects, and gradually manifest harmful effects on the brain from maternal/fetal complications in pregnancy, which manifest in new-born hyperbilirubinemia, mild disorders among children and adults such as dyslexia, and/or learning and memory deficiencies in the ageing process, and to significant neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease and multiple sclerosis.

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