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Cobalt as a hypoxia-like factor in humans and animals

Abstract
The aim of the article is to present selected aspects of the impact of cobalt on animal and human organisms from the point of view of links to hypoxia (hypoxia of various origins). The subject of the analysis is the issue of the influence of cobalt as a means of protection under hypoxic conditions at the following levels of body systems: tissue, cellular and molecular.

Keywords: cobalt, pollutants, heavy metals, lipid peroxidation, hypoxia, different resistance to hypoxia, oxidative stress.

Heavy metals are too well-known environmental pollutants of particularly dangerous effects on human health (Fisher, Langston 1968, Barceloux, 1999, Valko et al., 2005, Gill et al., 2012). Because of their wide usage in many industrial branches they are present everywhere in the air, water and soils (Barceloux, 1999, Linna et al., 2004, Ghio et al., 2012). Inadequate nutrition also may have added to heavy metals toxicity. Hard metal dust, of which occupational exposure is linked to an increased lung cancer risk, is proven to be genotoxic in vitro and in vivo (De Boeck et al., 2003). Possibly, production of active oxygen species and/or DNA repair inhibition are mechanisms involved.

Genotoxic potential (Magaye et al., 2012) of hard metal dust as given the recently provided proof for in vitro and in vivo, was suggested the mechanistic evidence of elevated production of active oxygen species and the epidemiological data on increased cancer risk. This adverse and putative beneficial effect was described for cobalt toxicology (Simonsen et al., 2012). Cobalt is used for the production of alloys and hard metal (cemented carbide), diamond polishing, drying agents, pigments and catalysts (De Boeck, 2003). Cobalt influences many metabolic processes causing great damage in many organs in dose-dependent manner and some cases was describes for myocardium injury (Jarvis et al., 1999).

Occupational exposure to cobalt may result in adverse health effects in different organs or tissues. Co (II) ions are genotoxic in vitro and in vivo, and carcinogenic in rodents. Co metal is genotoxic in vitro (Magaye et al., 2012). A notable toxic effect of cobalt intake is a severe and often lethal cardiomyopathy, seen in the 1960s among heavy beer drinkers after local breweries added cobalt chloride or sulfate to beer as a foam stabilizer (Mohiuddin et al., 1970; Seghizzi et al., 1994). In the lethal cases post-mortem analyses showed marked accumulation of cobalt in the myocardium. Co-

balt cardiomyopathy has also been seen following industrial exposure to cobalt (Jarvis et al., 1992). Linna et al. (2004) was described echocardiographic changes indicating altered left ventricular diastolic function, but without major cardiac dysfunction, among workers in an industrial plant.

The effects of cobalt are not only harmful, but may also be beneficial by synthesis of B_{12} vitamin for example. Cobalt is a relatively rare transition metal with properties similar to iron, chromium and nickel. Cobalt stimulates erythropoietin production and increases erythropoiesis, leading to increased oxygen-carrying capacity of the blood which is helpful under conditions of ischemia and tissue hypoxia. Moreover, preconditioning with cobalt salts akin to hypoxic preconditioning promotes tissue adaptation to hypoxia.

Myocardial ischemia has become the leading cause of mortality in western countries. From this biological perspective, myocardial necrosis is time-dependent and occurs when the action of the endogenous mechanisms of response to ischemia is finally overwhelmed (Lippi et al., 2006). Novel assay as described by Bar-Or D. et al. (2008) for the detection of myocardial ischemia (MI) involving the addition of $CoCl_2$ to plasma or serum has recently been proposed as the first sensitive marker for the diagnosis of myocardial ischemia (ischemic insult). During acute ischemic conditions, the metal binding capacity of albumin for transition metals, like copper, nickel and cobalt is reduced, generating a metabolic variant of the protein, commonly known as ischemia modified albumin (IMA).

The precise mechanism for IMA generation is yet unknown, though it appears that reactive oxygen species, produced during ischemia, might generate highly reactive hydroxyl free radicals, resulting in site-specific modification to the N-terminus of the albumin moiety. Generation of IMA as describes Xi et al., (2004) might thus be interpreted as an efficient endogenous mechanism of response to ischemia, preventing myocardial damage or limiting the extent of myocyte necrosis. In our investigation cobalt treatment may result in heart animals with low resistance to hypoxia via significantly decreasing superoxide dismutase and catalase activity, and glutathione peroxidase activity in high resistance group. For high resistance to hypoxia group animals cobalt treatment was demonstrated decreasing oxidatively proteins level in heart comparison control (Kurhaluk, Tkachenko, 2016).

Recent studies have provided insight into the interference of cobalt (Co^{2+}) with the oxygen sensors in the hypoxia response pathway present in almost all animal cells, contributing to the understanding of the possible carcinogenic effects of cobalt (Simonsen, 2012). Most of the studies on cobalt supplementation are focused on ischemia/reperfusion injury and also against ischemic injury (Matsumoto et al., 2003; Ohtomo et al., 2008). There is some of data on the efficacy of cobalt in facilitating preconditioning to hypobaric hypoxia and related ailments.

Cobalt preconditioning has been shown to attenuate hypoxia induced oxidative stress in rat brain (Shrivastava et al., 2008b). Cobalt chloride supplementation at low concentration as Endoh et al. (2000) reported improved cardiac contractile functions in hypoxia-reoxygenation in rats. Shrivastava et al., (2008a) have shown that cobalt preconditioning improves hypoxic tolerance of rats exposed to severe hypobaric hypoxia.

Different toxic and pharmacological agent influences may impact opposite changes in metabolism pathways (oxidative at first) in tissue of animals with genetically determined differences in the sensitivity to hypoxia. These changes are tissue-specific and depend on metabolic processes, redox properties, and prooxidant/antioxidant ratio in tissues. It may result in appropriate correction ensure. So far, the reasons for the physiologic reactions of hypoxia and hypoxia modulator agents on oxidative metabolism remain not totally understood. Also it remains unclear why not all humans and animals react in the same way on the identical factors (Kurhaluk et al., 2016).

Recent studies by Jones and Bergeron (2001) reported that prior exposure of new born rats to 8% hypoxia or $CoCl_2$ (60 mg/kg b.w.) protect the brain against ischemic injury but the mechanism was found to be different in both cases. It has reported that hypoxic preconditioning connect with the modulation of glucose transport and glycolysis by hypoxia and may contribute to the development of hypoxia induced tolerance. In contrast, preconditioning with cobalt chloride did not produce any change in HIF-1 target gene expression. It was sugges that different molecular mechanisms may be involved in the induction of tolerance by hypoxia and $CoCl_2$ in brain. However, some investigations (Endoh et al., 2000; Xi et al., 2004; Ohtomo et al., 2008) showed that the cytoprotective mechanisms elicited by cobalt chloride impact was mediated by expression of HIF-1α and its target genes. The differences could be attributed to dose-dependent manner, mode of treatment, and period of CoCl2 given to the animals.

Studies by Kalpana et al. (2008) reports the chemical preconditioning by cobalt for 7 days (12 mg Co/kg b.w., oral) i.p.1 h before exposing them to hypoxia significantly attenuated the vascular leakage induced by hypoxia. This was attributed to lower VEGF, ROS/NO levels, reduced NFκB activity and increased oxygen availability via Hif-1 signaling mechanisms. Further, higher levels of anti-inflammatory mediators namely TGFβ, IL-6, HO-1 and MT levels in cobalt preconditioned animals might also be responsible in attenuating the vascular leakage induced by hypoxia. Recently, Peters et al. (2005) reported that cobalt supplementation inhibited VEGF production induced by hypoxia in human.

At lower oxygen conditions, HIF-1α undergoes a stabilization process and induces activation of genetic sequences that promote efficient adaptations to hypoxia. On the basis of the evidence provided by the article of Xi et al. (2004), the in vivo generation of IMA might thus be interpreted as an efficient endogenous mechanism of response to ischemia, preventing myocardial damage or limiting the extent of myocyte necrosis.

Ingested Co is mainly translocated to the kidney; the liver has been reported to play an active role in rapidly removing Co ions from blood. In the liver cobalt is retained with a long biological half-life and causes a variety of toxic responses by the hepatic cells. Oxidative stress has been proposed as the most important mechanism of toxic action of cobalt in many organs of the body including heart, liver, spleen and kidney. The cobalt accumulation is similar in fed and ATP-depleted cells. Cobalt is known to bind to the globin moiety of hemoglobin. The results imply that during long-term cobalt exposure in vivo cobalt will be taken up practically irreversibly in the red cells during their 120 days life span (Simonsen et al., 2011).

There is evidence that soluble cobalt (II) cations exert a genotoxic and carcinogenic activity (Magaye et al., 2012) in vitro and in vivo in experimental systems but evidence in humans is lacking. The in vitro studies demonstrated that cobalt nanoparticles induced DNA strand breaks, micronuclei formation, chromosomal aberrations (aneuploidy, polyploidy and tetraploidy) and morphological transformation of mammalian cell lines. Cobalt nanoparticles exhibited higher genotoxicity than cobalt fine particles and ions. Cobalt nanoparticles were also shown to cause inflammation and oxidative stress. Investigators suggest that enhanced oxidative stress, inflammatory response and abnormal apoptosis may play major roles in the carcinogenicity of cobalt-based nanoparticle-induced carcinogenesis.

Experimental data (Lison et al., 2001) indicate some evidence of a genotoxic potential for cobalt metal in vitro in human lymphocytes but there is no evidence available of a carcinogenic potential. There is evidence that hard metal particles exert a genotoxic and carcinogenic activity in vitro and in human studies, respectively.

Scrolling the scientific literature for metabolic changes in animals and humans caused by hypoxia reveals a general problem. The study groups in general used different time-dosage regimens to perform their studies mostly in animals. This leads to different levels of oxidative stress in the subjects. Different levels of oxidative stress as well as different time-dosage regimens itself can have an adverse effect on oxidative metabolism. It is especially well-known that high levels of oxidative stress as they occur in heart injure at patients.

The results of this study provide evidence that the Co effect in the heart at doses 30 mg/kg bw, 3 h not related with LPO levels and TAA value and not connected with hypoxia resistance of rats. We haven't received any statistically significant differences LPO and TAA levels. It is important, that Co treatment at heart for HR animals was decreased OMP level (OMP KD) comparison control group.

We observed in our study relatively differ levels of Co treatment dependent low and higher resistance to hypoxia (Kurhaluk et al., 2016). Glutathione peroxidase activity was lower in high resistant to hypoxia (HR) animals group only at cobalt treatment. We demonstrated statistically decreased superoxide dismutase (SOD) and catalase (CAT) activities at cobalt impact in heart for low resistant to hypoxia (LR) animals only. These two types of animals (HR and LR) are described earlier as by two different functional and metabolic patterns (Tkachenko, Kurhaluk, 2016). They are associated with typical differences in activity of CNS and neurohumoral regulation, stress-activating and stress-limiting systems, oxygen-transporting function of the blood, and the state of membranes or receptors. Moreover, these parameters are coupled with energy exchange and functional activity of the respiratory change in animal tissues (Lukyanova, Kirova, 2010).

Study by (Lukyanova, Kirova, 2010) demonstrated that hypoxic preconditioning contributes to the development of immediate resistance, which is particularly pronounced in LR animals. These specimens do not exhibit signs of oxidative stress in tissues during the early posthypoxic period. By contrast, in HR animals, characterized by low ability for the resistance development, hypoxic preconditioning is followed by activation of free radicals production. Therefore, activation of these processes in

the early period of adaptation does not play a role in induction of immediate adaptive mechanisms.

Bondarenko et al. (2000) studied the behavioral reactions of rats with different resistance to hypoxia during different types of functioning of their dopaminergic systems. It has shown that the locomotor activity in the open field test did not correlate with rat resistance to acute hypobaric hypoxia; there was a correlation between this resistance and rat behavior during acute stress. Immobility was characteristic of rats with low and particularly medium resistance to hypoxia; this reaction can be abolished by antidepressants. By contrast, highly resistant rats were mainly hyperactive. The resistance to hypoxia was associated with extreme parameters of dopaminergic neuron functioning. In low-resistant rats locomotor stereotypia was maximal, while perioral stereotypia was the minimal; highly resistant rats were characterized by an opposite pattern, and medium-resistant rats occupied an intermediate position.

Recent studies by Jones and Bergeron (2001) reported that prior exposure of new born rats to 8% hypoxia or $CoCl_2$ (60 mg/kg b.w.) protect the brain against ischemic injury but the mechanism was found to be different in both cases. It has reported that hypoxic preconditioning connect with the modulation of glucose transport and glycolysis by hypoxia and may contribute to the development of hypoxia induced tolerance. In contrast, preconditioning with cobalt chloride did not produce any change in HIF-1 target gene expression. It was sugges that different molecular mechanisms may be involved in the induction of tolerance by hypoxia and $CoCl_2$ in brain. However, some investigations (Endoh et al., 2000; Xi et al., 2004; Ohtomo et al., 2008) showed that the cytoprotective mechanisms elicited by cobalt chloride impact was mediated by expression of HIF-1α and its target genes. The differences could be attributed to dose-dependent manner, mode of treatment, and period of CoCl2 given to the animals.

Summary, the changes caused by cobalt, are tissue-specific and depend on metabolic processes, redox properties, and prooxidant/antioxidant ratio in tissues. It may result in appropriate correction ensure.

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