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Review

Pro-inflammatory effects of metals in persons and animals exposed to tobacco smoke

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ABSTRACT

Metals present in tobacco smoke have the ability to cause a pro-oxidant/antioxidant imbalance through the direct generation of free radicals in accordance with the Fenton or Haber-Weiss reaction and redox properties. Metals can also interact with antioxidant enzymes (superoxide dismutase, catalase, glutathione peroxidase) and small molecular antioxidants (glutathione) through binding to —SH groups or by replacement of metals ions in the catalytic center of enzymes. Excessive free radicals production can induce an inflammatory response. The aim of this study was to review the information on the induction of inflammation by metals present in tobacco smoke such as lead (Pb), cadmium (Cd), arsenic (As), aluminum (Al), nickel (Ni) and mercury (Hg).

In cellular immune response, it was demonstrated that radicals induced by metals can disrupt the transcription signaling pathway mediated by the mitogen-activated protein kinase (induced by Pb), NLRP3-ASC-caspase 1 (induced by Ni), tyrosine kinase Src (induced by As) and the nuclear factor κB (induced by Pb, Ni, Hg). The result of this is a gene transcription for early inflammatory cytokines, such as Interleukine 1β, Interleukine 6, and Tumor necrosis factor α). These cytokines can cause leukocytes recruitment and secretions of other pro-inflammatory cytokines and chemokines, which intensifies the inflammatory response. Some metals, such as cadmium (Cd), can activate an inflammatory response through tissue damage induction mediated by free radicals, which also results in leukocytes recruitment and cytokines secretions. Inflammation generated by metals can be reduced by metallothionein, which has the ability to scavenge free radicals and bind toxic metals through the release of Zn and oxidation of —SH groups.

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Introduction

Tobacco consumption is a global problem. The country that consumes the largest amount of tobacco in the world is China [1]. According to the European Network for Smoking and Tobacco Prevention, tobacco consumption in Europe also remains high,

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especially in Central and Eastern Europe. Tobacco consumption in Poland stands at 1500–2000 cigarettes per person/year [2]. In Poland, 25% of women and 42% of men are active smokers [3]. Smoking is a social problem among youths. The Global Adult Tobacco Survey has shown that the percentage of current smokers in Poland aged 15 and above is 36.9% for males and 24.4% for females. Among all adults, 27% are current smokers [4]. Cigarette smoking increases the risk of circulatory disease and cancer of the lung or bronchus, urinary bladder, prostate, colon, rectum and pancreas, which can lead to death [5,6]. Tobacco use kills approximately 5–6 million people annually worldwide and 69,000 people in Poland every year [7,8]. On the basis of current smoking patterns, the number of annual deaths due to smoking will rise to around 10 million by 2030 [7]. Thus, cigarette smoking remains a very important global problem in respect of numbers of smokers and smoke substances present in the environment.

Cigarette smoke can induce an adverse effect in the organism, including by causing oxidative stress. Reactive oxygen species (ROS) production in the organism of humans or animals, including superoxide radical, hydrogen peroxide or hydroxyl radical, is related to the presence of metals in tobacco smoke; indeed, over thirty different metals, such as arsenic, lead, cadmium, nickel, mercury, aluminum, polonium and zinc were identified in studies of smoke [9–11]. The toxic effect of these metals was related to their ability to interfere in cellular processes, because metals can disturb biochemical reactions and cellular homeostasis by interacting with signaling proteins and DNA repair [12]. It was shown that metals present in smoke had pro-oxidant properties. They can generate ROS and reactive nitrogen species and impair antioxidant mechanisms in cells. This results in a pro/antioxidant imbalance and the induction of oxidative stress, which is responsible for oxidative damage in tissues and the development of inflammatory processes [13–16]. In addition, toxic metals present in tobacco smoke can induce leukocytes recruitment into the tissue, its activation, pro-inflammatory cytokines secretion and can amplify tissue inflammatory response [17]. A summary of the recent literature on inflammatory response induced by tobacco smoke metals is shown in Table 1 [13–31].

Pro-inflammatory effect of lead (Pb)

One of the metals present in tobacco smoke is lead (Pb). A positive correlation of the presence of this metal and the intensity of smoking has been identified [32]. The pro-inflammatory effect of this component was related to its ability to cause oxidative stress due to the generation of free radicals and the weakening of cellular antioxidant mechanisms [33]. Mechanisms to stimulate the production of free radicals by Pb are not well known. The first of these assumed that the production of ROS can be an effect of Pb-induced δ-aminolevulinic acid dehydratase (ALAD) (EC 4.2. 1.24) inhibition, the enzyme which catalyzes a step of heme synthesis involving the condensation of two molecules of δ-aminolevulinic acid (ALA) to porphobilinogen [10,34]. As a result of tautomerization, the formation of the ALA-enol form – an electron donor for molecular oxygen – was observed [35]. The process of hydrogen peroxide (H_2O_2) and superoxide anion ($O_2^{\bullet -}$) formation can be accompanied by oxyhemoglobin (oxyHb) oxidation and the formation of methemoglobin (metHb) and ALA radicals (Fig. 1) [10,35]. H_2O_2 and $O_2^{\bullet -}$ can interact with each other to form hydroxyl radicals ($HO^{\bullet -}$), which are the most reactive of all ROS [10]. ALA, as easily oxidized α-aminoketone, can be also oxidized by hemoglobin forms as a Fenton-type reagent [35,36]. It was shown that the concentration of ALA correlated with oxidative stress intensity, because Pb directly induced oxyHb oxidation and co-oxidation oxyHb with ALA [35]. Pb can also cause an inhibition of ferrochelatase (EC 4.99.1.1),

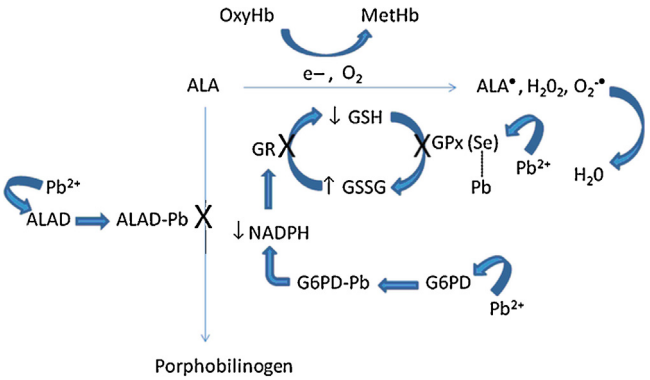

Fig. 1. The disruption of enzymes activity in erythocytes as a result of exposure to Pb ions.
ALA: δ-aminolevulinic acid; ALAD: δ-aminolevulinic acid dehydratase; oxyHb: oxyhemoglobin; MetHb: methemoglobin; GSSG: oxidized glutathione; GPx: glutathione peroxidase; GR: glutathione reductase.
Pb causes the inhibition of ALAD, catalyzing the condensation of two molecules of ALA to porphobilinogen. This leads to ALA accumulation and ALA-enol forms are formed as a result of tautomerization. The enol forms of ALA are an electron donor for the molecular oxygen and can easily generate H_2O_2 and $O_2^{\bullet -}$. ALA enol forms can also interact with oxyHb, which leads to the transfer of electrons from oxyHb to oxygen, resulting in the formation of metHb, ALA radical, H_2O_2 and $O_2^{\bullet -}$. Pb can also inactivate G6PD by binding to thiol groups of enzyme, which leads to a decrease in the amount of formed NADPH. This results in GR inhibition converting GSSG to GSH in the presence of NADPH oxidase using NADPH as a substrate. Pb can also inactivate GPx by binding to Se, which is required for the proper functioning of GPx and the formation of Se-Pb complexes, which leads to a decrease in GPx activity and further accumulation of ROS.

an enzyme catalyzing the incorporation of ferrum (Fe) into protoporphyryn IX during hemoglobin synthesis [37,38]. This can result in an increase in Fe concentration in serum. Increased Fe levels can give rise to oxidative stress, because Fe is known as a metal, which induces $HO^{\bullet -}$ production by the Fenton reaction [39]. $HO^{\bullet -}$ radicals can react with cysteine, containing proteins, to yield thiyl radicals. These may interact with cell-reducing agents such as glutathione (GSH). As a result of this, intermediates are produced, which react with molecular oxygen to form $O_2^{\bullet -}$ [39].

A decreased volume of reduced glutathione after exposure to Pb can also be explained by the inactivation of glutathione reductase (GR) (EC1.6.4.2). This enzyme is responsible for the conversion of oxidized glutathione (GSSG) to a reduced form (Fig. 1) [10]. The conversion of GSSG to GSH occurred in the presence of reduced nicotinamide adenine dinucleotide phosphate (NADPH) oxidase derived from the pentose phosphate cycle. It is believed that Pb can inhibit the activity of one of the main cycle enzymes–glucose-6-phosphate dehydrogenase (G6PD) (EC 1.1.1.49) as a result of binding to thiol groups of enzymes, thereby reducing the amount of formed NADPH. In this way, less GSSG to GSH was converted and antioxidant mechanisms were reduced. There is no consensus on the effect of Pb on G6PD – in the literature information can also be found indicating that Pb caused an increase in the activity of G6PD [39].

Some studies have demonstrated that Pb reduces the activity of antioxidant enzymes, such as superoxide dismutase (SOD) (EC 1.15.1.1), catalase (CAT) (EC 1.11.1.6) and glutathione peroxidase (GPx) (EC 1.11.1.9). It was shown that Pb can bind to both heme – a structural component of CAT – and selenium, which is required for the proper functioning of GPx [10]. Pb also replaced cooper (Cu) and zinc (Zn) in the Zn/Cu SOD, resulting in the inhibition of the enzyme and causing a reduction in levels of antioxidants such as GSH [39]. The metal's ability to directly bind to thiol groups can explain its strong binding to GSH, leading to GSH inactivation. GSH could not play its role as an antioxidant and there was an oxidant–antioxidant imbalance in cells [10].