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SCIENTIFIC WORK

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POTENTIAL PATHOPHYSIOLOGICAL MECHANISMS OF ULTRAFINE PARTICLE TOXIC EFFECTS IN HUMANS

Epidemiological and clinical studies suggested the association of the particulate matter ambient air pollution and the increased morbidity and mortality, mainly from respiratory and cardiovascular diseases. The size of particles has great influence on their toxicity, because it determines the site in the respiratory tract where they deposit. The most well established theory explaining the mechanisms behind the increased toxicity of ultrafine particles (UFP, < 0.1 μm) is that it has to do with the increased surface area and/or the combination with the increased number of particles. Biological effects of UFP are also determined by their shape and chemical composition, so it is not possible to estimate their toxicity in a general way. General hypothesis suggested that exposure to inhaled particles induces pulmonary alveolar inflammation as a basic pathophysiological event, triggering release of various proinflammatory cytokines. Chronic inflammation is a very important underlying mechanism in the genesis of atherosclerosis and cardiovascular diseases. UFP can freely move through the circulation, but their effects on the secondary organs are not known yet, so more studies on recognizing toxicological endpoints of UFP are needed. Determination of UFP toxicity and the estimation of their internal and biologically active dose are necessary for the evidence based conclusions connecting air pollution by UFP and human diseases.

Key words: ultrafine particles, human health, pathophysiological mechanisms, chronic inflammation, respiratory disease, cardiovascular disease.

Over the last decade, numerous epidemiological and clinical studies have suggested the association between the ambient air pollution and the increased morbidity and mortality, mainly from respiratory and cardiovascular diseases [1-6]. Some air pollutants, like carbon monoxide, sulfur dioxide, nitrogen oxides, ozone, lead, and persistent organic pollutants, are well known toxic agents, but there is a growing interest in the particulate matter (PM) deleterious effects. A particulate matter is a generic term for the type of air pollutants consisting of a complex and varying mixture of particles suspended in the breathing air, which vary in size and composition and are produced by a wide variety of natural and anthropogenic activities [7]. Major sources of the particulate matter air pollution are factories, power plants, motor vehicles, fires and construction activities. The size of particles varies and according to the aerodynamic diameter of a particle different categories have been defined. The coarse particle size ranges from 2.5 to 10 μm, and the fine particle size is 0.1-2.5 μm. Ultrafine particles (UFP) are those with diameters smaller than 0.1 μm [8]. This categorization has a great importance from the medical point of view. Beside the chemical structure and their number concentration in the air, the size of a particle has great influence on their toxicity. The size of the particles determines the site in the respiratory tract that they deposit. Coarse particles mainly stay at upper respiratory airways, while smaller particles reach lower, to terminal airways and alveoli. The strongest connections are seen for the respiratory and cardiac disorders. The aim of this paper is to review the possible pathophysiological mechanisms by which the ultrafine particles may affect the human health.

ROUTES OF EXPOSURE

Polluted air and water are the sources of possible toxic ultrafine particles, so the main routes of the general population exposure to ultrafine particles are

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inhalation and ingestion, while dermal absorption is insignificant. There are studies indicating that in some cases the air pollution contributes to a great extent to the contamination of food and water, making ingestion the main route of the exposure [9]. Because of their small size UFP are able to reach general circulation and deposit into different tissues producing possible deleterious effects [10,11].

POSSIBLE MECHANISMS OF UFP EFFECTS

General hypothesis proposed by Seaton *et al.* [12] suggested that the exposure to inhaled particles induces alveolar inflammation as a basic pathophysiological event. Inflammation is a complex defense reaction of the organism, and some characteristic cellular and humoral markers of the body response could be used as the measure of its occurrence and intensity. Thus, the exposure to inhaled particles produces the increase in the blood concentration of C-reactive protein (CRP), fibrinogen, and proinflammatory cytokines, like IL-6 and IL-1 beta. UFP cause more inflammation when inhaled and deposited in the lung than larger particles of the same material. They possess more ability to produce reactive oxygen species [13]. *In vitro* studies have also shown that UFP can stimulate the expression of proinflammatory genes in epithelial cells and alveolar macrophages. It is probably caused by their ability to increase intracellular calcium levels and, in this way, to inhibit phagocytosis [14]. There are theories trying to explain the mechanisms behind the increased toxicity of ultrafine particles. The most well established theory is that it has to do with the increased surface area and/or combination with the increased number of particles [15,16]. However, biological effects of UFP are also determined by their shape and chemical composition, so it is not possible to estimate their toxicity in a general way. Some low toxic UFP may absorb substances with higher toxicity, like metals and gases, or may facilitate a transition of adenoviral infection. On the other hand, the inhibition of phagocytosis may be connected with the increased susceptibility to bigger particles or to a bacterial infection. The air pollution research on coarse particles, especially in occupational medicine, has established clear links between the increase of the particular matter in the air and lung diseases. The increase in a particle concentration in the air may overload the lung and the phagocytes that are responsible for the elimination of those particles. This overloading of the lungs causes inflammation of the surrounding tissue, also known as oxidative stress. In case of chronic exposure to UFP, persistence of a high inflammatory response may damage the lung tissue with a clinical consequence manifested as the exacerbation of preexisting lung disease and/or the development of asthma, chronic bronchitis, lung fibrosis or cancer [17,18]. The degree to which UFP contribute to these diseases has not been established yet.

Inhaled UFP are also able to translocate trough the circulation from the point of intake into the lung to the secondary organs [19], and there is a possibility of many different interactions with biological systems of the body. If the size of the foreign substances entering the bloodstream is great enough, they are removed by phagocytes, but being smaller than particles phagocytes could recognize, UFP can freely move through the circulation. They can pass the blood-brain barrier entering the central nervous system [20], as well as other organs. The effects ultrafine particles cause in the secondary organs are not known yet. However, there are some evidences of their direct toxic effect. When instilled into the cardiac vasculature, UFP produce worsening of the cardiac function by decreasing the cardiac coronary flow and contractility [21]. So, there is a possibility that except for starting the pathophysiological events in the lungs, UFP could reach other organs through the circulation and produce direct effects there.

The linkage between the airway inflammation with the cytokine/chemokine release and an autonomic stress response caused by inhalation of UFP and cardiovascular disorders has not been directly demonstrated in humans. Some links between the pulmonary and cardiovascular response to UFP are suggested. There is growing evidence from animal models that the airway inflammatory reaction may trigger a systemic inflammation and hypercoagulability [22]. The effect of inflammation, with the increased ROS, proinflammatory cytokines, CRP and fibrinogen in the bloodstream is one of the proposed pathophysiological mechanisms of UFP deleterious effects on the cardiovascular system [12]. Subsequently, a cascade of physiological responses may follow, including disturbances in the blood rheology facilitating thrombosis and the development of atherosclerotic plaques. The increase in the blood coagulability is connected with a higher risk of cardiovascular disorders. Chronic inflammation is very important underlying mechanism in the genesis of atherosclerosis. Atherosclerosis is characterized by the formation of plaques within blood vessels, which may cause their narrowing or obstruction, with the consequent tissue hypoxia or necrosis. Clinically, it may be manifested by ECG changes of myocardial ischemia, like ST segment depression, or like more serious disorders, including angina pectoris, myocardial infarction, and even cardiac arrest and death.

The alterations in the autonomic nervous system induced by pulmonary reflexes may, to some extent, influence a vascular tonus and the cardiac impulse conduction, which may be manifested as fluctuations in the blood pressure and the heart rate including the occurrence of arrhythmias. The results of the studies investigating disturbances of a cardiac autonomic nervous system are controversial [23-26] but there are findings supporting the notation that air pollution is capable of altering autonomic balance in a manner that favors significant tachyarrhythmias. The underlying responsible mechanisms remain unclear, but may involve the activation of pulmonary neural reflex arcs, a direct effect of pollutants on cardiac ion channels, or the consequences of the heightened systemic inflammatory state [27]. However, a clinical significance of those, comparing with other well recognized risk factors for cardiovascular diseases like age, hypertension, hyperlipidemia and diabetes is probably much lower.

Except the non-specific proinflammatory effect of UFP, their ability to affect human health also depends on their chemical structure. It is well recognized that metals, apart from producing oxidative stress, can substitute diverse polyvalent proteins cations and impair their function. Some other substances, like dioxin, also may alter the metabolism by inducing a number of important metabolic enzymes [28] or act at the DNA level altering the expression of certain genes [29].

CONCLUSION

The current knowledge base of the risks of ultrafine particles to human health is primarily based on epidemiological studies of air pollution indicating the increased morbidity and mortality mainly from respiratory and cardiovascular diseases. Some basic biological mechanisms of UFP effects are suggested upon experimental studies *in vitro* and *in vivo*, on animal models and human volunteers, but their pathophysiological relevance for the development of a disease needs to be proved by further research. From the clinical toxicology point of view, more studies on recognizing toxicological endpoints of UFP are needed. The determination of various UFP toxicity and the estimation of their internal and biologically active dose, as well as better understanding of their pathophysiological pathways are necessary for the evidence based conclusions connecting the air pollution by UFP and humans diseases.

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