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Air pollution ultrafine particles: toxicity beyond the lung

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Abstract. – *Background:* **Ultrafine particles or nanoparticles (UFPs or PM0.1) are the fraction of ambient particulates with an aerodynamic diameter smaller than 0.1 µm.**

Currently UFPs are emerging as the most abundant particulate pollutants in urban and industrial areas, as their exposures have increased dramatically because of anthropogenic sources such as internal combustion engines, power plants, incinerators and many other sources of thermo-degradation.

Ultrafine particles have been less studied than PM2.5 and PM10 particulates, mass concentrations of particles smaller than 2.5 and 10 µm, respectively.

Objective, Evidence and Information Sources: **We examined the current scientific literature about the health effects of ultrafine particles exposure.**

State of the Art: **UFPs are able to inhibit phagocytosis, and to stimulate inflammatory responses, damaging epithelial cells and potentially gaining access to the interstitium. They could be responsible for consistent reductions in forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC) in patients with asthma. Chronic exposure to UFPs can produce deleterious effects on the lung, also causing oxidative stress and enhancing pro-inflammatory effects in airways of COPD patients.**

Cardiovascular detrimental consequences due to UFPs exposure have observed in epidemiological studies, and could likely be explained by translocation of UFPs from the respiratory epithelium towards circulation and subsequent toxicity to vascular endothelium; alteration of blood coagulation; triggering of autonomic nervous system reflexes eventually altering the cardiac frequency and function.

Once deposited deeply into the lung, UFPs – in contrast to larger-sized particles – appear to access to the blood circulation by different transfer routes and mechanisms, resulting in distribution throughout the body, including the brain, with potential neurotoxic consequences.

Perspectives and Conclusions. **UFPs represent an area of toxicology of emerging concern. A new concept of environmental medicine would help in understanding not only the environmental mechanisms of disease, but also in developing specific preventive or therapeutic strategies for minimizing the dangerous influence of pollution on health.**

Key Words:

Nanoparticles, Lung injury, Cardiovascular disease, Health effects.

Introduction

The incidence and the prevalence of respiratory diseases have increased relentlessly along with air pollution and particulates are emerging as the most dangerous pollutants for their adverse health effects going far beyond the simple toxicity to the lung[1].

Particulates are a mixture of solid and liquid tiny particles in the air of different origin, size and composition: various classifications and terminologies have been used to define particle size ranges. The division most commonly used is between fine and coarse particles, with the boundary between these two fractions being widely accepted as 2.5 µm. Fine particles are smaller than this and coarse particles are larger.

The terminology that has been used in the wording of the ambient air quality standards, and also for characterization of indoor and outdoor particle mass concentrations includes the $PM_{2.5}$ and PM_{10} fractions. $PM_{2.5}$ (*fine particles*) is the mass concentration of particles with aerodynamic diameters smaller than 2.5 µm. PM_{10} (*coarse particles*) is the mass concentration of particles with aerodynamic diameters smaller than 10 µm. In most urban and industrial environments both coarse and fine particles are likely to be prominent, the former primarily derived by construction and demolition activities, mining and caving

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operations, and entrainment of road dust into the air, the latter primarily produced by combustion of fossil fuels from power plants and vehicles.

Ambient particles include also ultrafine particles or nanoparticles (UFPs or $PM_{0.1}$) which have an aerodynamic diameter smaller than 0.1 μm.

Another classification is into submicrometre particles, which are smaller than 1 μm, and supermicrometre particles, which are larger than 1 μm.

There have been references made in the literature to PM_1 or $PM_{0.1}$ fractions, which imply mass concentrations of particles smaller than 1 and 0.1 micrometres, respectively. These terms should be used with caution, as particles below 1 micrometre, and, even more importantly, those below 0.1 micrometres, are more commonly measured in terms of their number rather than their mass concentration. In fact, since ultrafine particles reach high concentrations in terms of their numbers but their mass is often very small, measurements of particles in ultrafine or broader, submicrometre ranges are more commonly based on particle number rather than mass concentration. Furthermore, the ultrafine particle size range tends to dominate particle number size distribution whereas the coarse particle size range tends to dominate the particle mass size distribution.

Generally UFPs are combustion derived, such as diesel exhaust particles. Their chemistry is derived from the combustion and pyrolysis processes, whereby combustion concentrates transition metals and pyrolysis generates organic compounds, along with elemental organic carbon particles. The chemical composition of UFPs varies greatly and depends on numerous geographical, meteorological, and source-specific variables, including inorganic components (sulfates, nitrates, ammonium, chloride, trace metals), elemental and organic carbon, crystal materials, biological components (bacteria, spores, pollens), and adsorbed volatile and semivolatile organic compounds. In addition, ambient particles, when mixed with atmospheric gases (ozone, sulfur and nitric oxides, and carbon monoxide [CO]), can generate ambient aerosols. Currently ultrafine particles are emerging as the most abundant particulate pollutants in urban and industrial areas, as their exposures have increased dramatically because of anthropogenic sources such as internal combustion engines, power plants, incinerators and many other sources of thermo-degradation.

Fine particulates ($PM_{2.5}$) have been associated with both respiratory and cardiovascular diseases and with lung cancer[2-9]. It has been also demonstrated a strong evidence of a relation between $PM_{2.5}$ and hospitalizations for both respiratory and cardiovascular diseases[10,11].

Additionally, exposure to $PM_{2.5}$ is associated with increased daily mortality for all-causes and for single subgroups, including respiratory diseases, cardiovascular diseases, diabetes[12].

Two large cohort studies in the USA, the Six City Study[2] and the American Cancer Society study[3], showed highly significant associations of all-cause and cardiopulmonary mortality rates with increasing levels of fine particles. Results of these two studies were so relevant that led the Environment Protection Agency to place regulatory limits on $PM_{2.5}$ and revise the National Ambient Air Quality Standards. The risk for various outcomes has been shown to increase with exposure, but so far epidemiological evidences do not suggest a threshold below which any adverse health effects would be avoided.

In fact, the lower range of concentrations at which adverse health effects have been demonstrated is not greatly above the background concentration in urban areas. The European Respiratory Society[13] has published recently its concern about the mismatch between European Union policy and the best scientific evidence on adverse health effects of particulates, stating that implementing stringent air pollution legislation would result in life expectancy gains and pointing out that the benefits would outweigh the costs.

A recent study has directly evaluated the changes in life expectancy associated with differential changes in fine particulate air pollution that occurred in the United States during the 1980s and 1990s[14], demonstrating that a reduction in exposure to $PM_{2.5}$ contributed to significant and measurable improvements in life expectancy.

Ultrafine particles have been less studied than $PM_{2.5}$ and PM_{10} particulates. Relatively few epidemiologic studies have examined the health effects of ultrafine particles exposure because most ambient air monitoring measures particle mass, and there is relatively poor correlation between particle mass (dominated by PM_{10} and $PM_{2.5}$) and particle number (dominated by UFPs). It has been showed that the smaller the size of the particles the more dangerous the health effects[4] and ambient UFPs concentrations have been clearly associated with mortality[15] (Figure 1).

Compared with fine particles at similar mass concentrations in the air, UFPs have a much high-

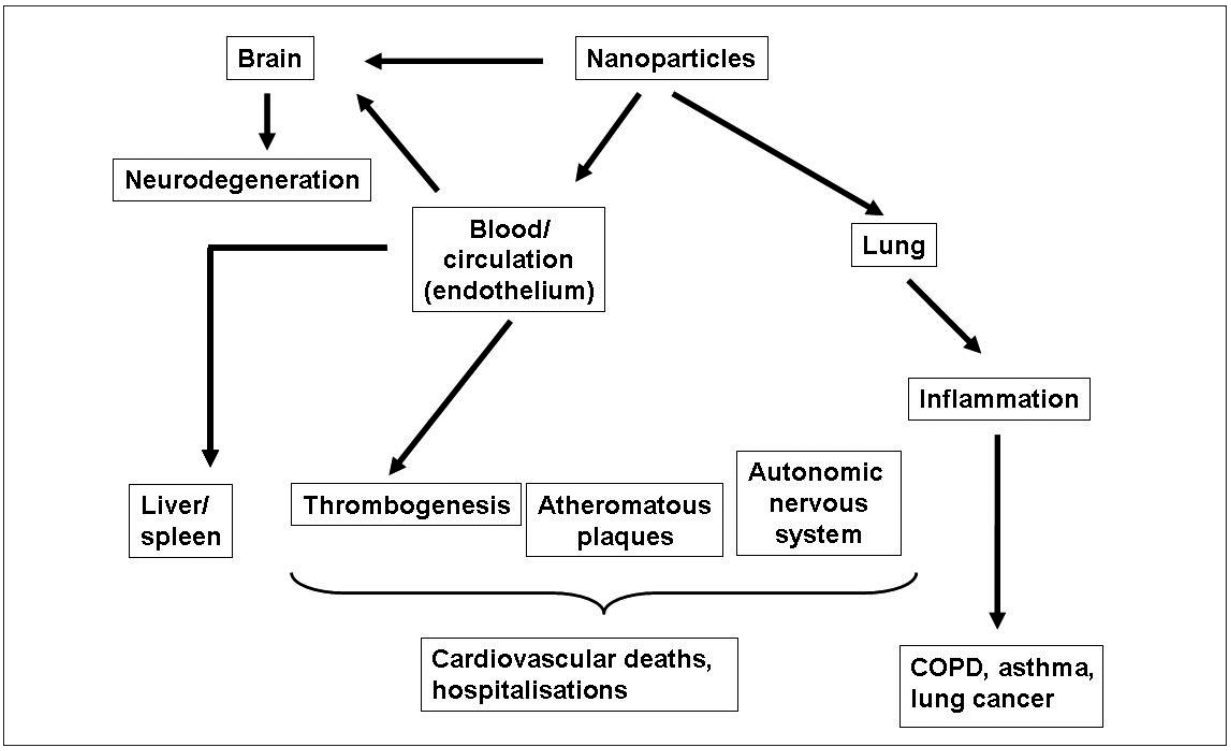

Figure 1. Systemic health effects of UFPs.

er number concentration and surface area than larger particles[16], enhanced oxidant capacity[17,18], greater inflammatory potential[16] and higher pulmonary deposition efficiency[19,20].

The UFPs are not filtered out by the nose and bronchioles and their size allows them to be breathed deeply into the lungs where they are able to penetrate alveolar epithelium and enter the pulmonary interstitium and vascular space to be absorbed directly into the blood stream[21].

The body does not have efficient mechanisms for clearing the deeper part of the lung as only a tiny fraction of natural particles will be as small as this. The UFPs are highly chemically reactive due to property of their small size and large surface area[22], as surface molecules depend on the particle size, increasing exponentially when particle size decreases <0.1 μm. Moreover, they carry large amounts of toxic compounds on their surfaces[23]. For example, in incinerators air emissions, heavy metals, dioxins, hydrocarbons and other organic chemicals can adhere to UFPs surface and increase their toxicity[24].

Pulmonary Toxicity

Inhalation of UFPs causes inflammation via oxidative stress and activation of redox-sensitive transcription factors (i.e., mitogen-activated protein kinase and nuclear factor-κB[25,26]. Considering particles in the ultrafine size range, lung inflammation is a consequence not of the mass, but of the number of particles[27]. The respiratory tract is subjected to daily low mass concentrations of particles, but high number concentrations[27,28].

It is estimated that on a so-called "low pollution" day (over 24 h), an adult human will inhale approximately 200 billion particles, half of which will be deposited in the lung, without apparent harm[27]. These huge numbers of particles are contained in a very small mass (400 μg).

During pollution episodes, where the average particle mass rises to 50 μg/m^3, the mass of inhaled particles associated with adverse respiratory effects may contain 2000 billion particles[27]. Although the physicochemical properties differ greatly among different types of UFPs, they have a soluble component and release transition metals or organics as their primary pro-inflammatory mechanisms. When the transition metals and polycyclic aromatic hydrocarbons (PAHs) interact with the lining fluids of the lung, they undergo cycling redox reactions that produce reactive oxygen species (ROS) (e.g., superoxide anions, hydroxyl radicals)[27].

Carbon particles derived from combustion processes are the most numerous particles in the ultrafine range. Carbon particles aggregate easily into clusters containing substances like iron, other transition metals, volatile organic compounds and polycyclic aromatic hydrocarbons, which all have been associated with the inflammatory reaction caused by particles[29-33].

Independently of their chemical composition, the inflammatory properties of ultrafine particles are mediated by their large numbers, small size and high penetration rate into the interstitium[34], as they are not readily and easily phagocytized by alveolar macrophages[35]. UFPs have a deleterious effect on phagocytosis of alveolar macrophages[36]. The effect is not apparently mediated by soluble mediators but by ultrafine particle cell contact, which rapidly stimulate the opening of membrane calcium channels in macrophages, leading to a substantial increase in the intracellular calcium levels[37-39]. The role that these calcium fluxes play in the inhibition of phagocytosis needs more investigations, but increased calcium stimulates transcription of pro-inflammatory genes in macrophages as well as in epithelial cells[40]. Thus the adverse effects of ultrafine particles may be mediated in part by their ability to inhibit phagocytosis, allowing ultrafine particles and other particles that deposit along with them to persist unphagocytosed in the lung, and stimulating inflammatory responses, damaging epithelial cells and potentially gaining access to the interstitium.

Recently it has been observed that the exposure to the diesel traffic is responsible for a consistent reduction in forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC) in persons with asthma[41].

It has been suggested that the high number of particles below 0.1 μm in diameter (UFPs) may be responsible for the adverse respiratory effects of particulate air pollution and be more strongly associated with decrease in lung function in asthmatic patients[42-44]. In asthmatic patients UFPs were associated with a decrease in peak expiratory flow and increase in self-reported symptoms[43], daily variations of PEF[45], asthma medication use and symptoms[46].

There is increasing evidence that ultrafine particulate pollutants exert adverse pulmonary effects by generating airway inflammation as well as acting as adjuvants for IgE production in the immune system[47,48], explaining the increased asthma prevalence and airway hyper-reactivity in response to elevated levels of ambient particulate matter[47,48].

The combination of mucosal stimulation with diesel exhaust particles (DEP) and ragweed allergen was shown to be capable of driving *in vivo* isotype switching to IgE in humans with ragweed allergy[49]. These results further support the concept that increasing environmental DEP with unchanged levels of allergen could be a factor in the increasing clinical sensitization. It is also possible that DEP may not only enhance isotype switching and IgE production but, in conjunction with an antigen, it may also help to induce a *de novo* specific IgE mucosal response. Experimental data show that exposure to ultrafine carbon particles before allergen challenge exerts strong adjuvant effects on the elicitation phase of the allergic response[50,51]. Allergen' sensitized subjects may therefore be more susceptible to adverse respiratory health effects of ultrafine particles.

Cronic exposure to UFPs can produce deleterious effects on the lung leading to chronic obstructive pulmonary disease (COPD)[52]. Ultrafine particles and transition metals they carry on their surface cause oxidative stress and this may enhance pro-inflammatory effects in airways of COPD patients. The generation of oxidative stress directly from the ultrafine and transition metal component of particulates and indirectly from the recruitment to the airspaces and activation of blood leukocytes, could enhance the already increased oxidant burden which occurs in the lungs of patients with COPD[53] and cause transcription of pro-inflammatory genes *via* redox sensitive transcription factors, such as nuclear factor kappa B (NF-B) activation and histone acetylation[54]. Infection with virus and other pathogens may also interact with oxidative stress to promote exacerbations, as alveolar epithelial cells upregulate IL-8 messenger ribonucleic acid (mRNA) and release increased IL-8 protein in response to particles[55].

A recent study suggests that elevated concentrations of air pollution are associated with changes in some blood markers of inflammation and coagulation (e.g., fibrinogen, E-selectin) in patients with COPD[56].

Patients with obstructive lung disease have a higher minute ventilation than healthy people, because of increased dead space ventilation. The increased minute ventilation and hyperinflation that are characteristic of COPD and even mild asthma, enhance diffusional deposition of UFPs

in the distal airways and alveoli[57-59]. Thus, people with COPD and asthma have a higher total respiratory dose of UFPs for a given exposure, which may contribute to their increased susceptibility to the health effects of air pollution.

Numerous epidemiological studies in the past 30 years found a strong exposure-response relationship between particulates and long-term or cumulative health effects as lung cancer, together with cardiopulmonary morbidity and mortality[60]. These effects are stronger for fine and ultrafine particles because they can penetrate deeper into the airways of the respiratory tract and can reach the alveoli in which almost 50% are retained in the lung parenchyma, where exert genotoxicity and carcinogenic mechanisms[61-63].

The process involved in particle-induced genotoxicity remains poorly understood, because the particles are uniquely complex owing to their physicochemical characteristics. There is evidence that diesel exaust particles (DEP)[64], carbon blacks particles (CB)[65], and coal fly-ash (FA)[66] are carcinogenic in humans. DEP consist of a carbon core with adsorbed polycyclic aromatic hydrocarbons (PAHs) and transition metals[67]. Genotoxicity may be induced by the direct interaction of PAHs, which are known to cause DNA adducts[68,69]. Alternatively, the transition metals may induce ROS, which results in DNA strand breakage[70]. Carbon black is generally devoid of adsorbed organics and metals and, thus, its genotoxicity is most likely an effect of the particle overload phenomenon, but some research has revealed the formation of the oxidative DNA lesion 8-hydroxydeoxyguanosine (8-OH-dG)[65,71]. Studies investigating the genotoxicity of FA have determined a role for particle size and iron release leading to radical generation and oxidative stress[72].

Cardiovascular Toxicity

Epidemiologic studies have demonstrated that exposure to particulate air pollution is an important risk factor in the development of cardiovascular disease[73-75]. Several important cardiovascular effects have been documented, including disruption of autonomic nervous system activity by decreased heart rate variability[76,77], arterial vasoconstriction[78], cardiac arrhythmias in patients with implantable defibrillators[79], myocardial infarction[80] and other cardiac events requiring hospitalization[81], and exacerbation of ST-segment changes in experimental models of myocardial infarction[82].

In a recent work ultrafine particle-exposed mice exhibited significantly larger early atherosclerotic lesions than mice exposed to $PM_{2.5}$ or filtered air[83]. Exposure to ultrafine particles also resulted in an inhibition of the antiinflammatory capacity of plasma high-density lipoprotein and greater systemic oxidative stress as evidenced by a significant increase in hepatic malondialdehyde levels and upregulation of Nrf2-regulated antioxidant genes[83].

In a recent investigation, the Exposure and Risk Assessment for Fine and Ultrafine Particles in Ambient Air or so called ULTRA study[84], Authors followed a cohort of patients with established coronary heart disease with biweekly submaximal exercise tests over a 6-months period. They observed that the risk of developing ischemia during exercise was significantly elevated at 2 days after exposure to increased environmental levels of fine particulate air pollution, with the strongest effects for $PM_{0.1}$ and $PM_{2.5}$. The importance of this observation is that it highlights myocardial ischemia as a significant potential mechanism responsible for the adverse cardiac outcomes associated with poor air quality. It remains unclear whether ischemia contributes to the adverse cardiac outcomes observed in epidemiological studies through a mechanism related to plaque rupture leading to an acute coronary syndrome and/or to precipitation of life-threatening arrhythmias.

Recently in has been observed an increase in plasma soluble CD40ligand (sCD40L, also known as CD154, a marker for platelet activation that can cause increased coagulation and inflammation) and a reduction in platelet counts, in association with exposure to ultrafine particles, in patients with coronary heart disease (CHD)[85]. The increased plasma sCD40L levels support the hypothesis that higher levels of ambient air pollution lead to an inflammatory response in patients with CHD thus providing a possible explanation for the observed association between air pollution and cardiovascular morbidity and mortality in susceptible parts of the population[85].

The ULTRA study focused on patients with known cardiac disease, but it would also be important to determine whether other patient populations are also susceptible to poor air quality, such as those with diabetes[86] or pulmonary disease. An increase in stroke mortality among the elderly in association with daily variations in $PM_{2.5}$, and to a lesser extent with ultrafine particles and CO has been found[87-89].

Nanoparticles have a diameter of less than 0.1 μm, and while constituting a small fraction of the total mass of ambient particulate matter, they represent a substantial proportion in terms of particle number. Toxicologists suggest that the nanoparticulate component of ambient particulate matter is the most potent and likely to be responsible for adverse cardiovascular health effects[90].

The precise mechanism by which air pollution influences cardiovascular risk has not been fully understood yet. However, a number of interesting hypotheses have been proposed to explain how inhaled particles could interact with the cardiovascular system[73,85,91]. The traditional view is that inhaled particles provoke an inflammatory response in the lungs, with consequent release of prothrombotic and inflammatory cytokines into the circulation, which can affect the stability of the atheromatus plaques (fatty deposits) in the walls of arteries[92-94]. These compounds may then trigger a cascade of reactions: initial local production by macrophages and activated alveolar cells of pro-inflammatory cytokines, such as interleukin-6[95], and increased expression of endothelin[96], whose elevated systemic levels are associated with a poor cardiovascular prognosis[97]. This induced systemic inflammation may be reflected by elevated C Reactive Protein (CRP)[98] which is significantly and independently associated with the risk of coronary heart disease[95,99]. Other studies have shown increased levels of fibrinogen and platelets[100], altered blood viscosity[78], modification of the adhesive properties of red blood cells with peripheral sequestration, and altered vascular tone[78].

Recent evidences suggest also that inhaled insoluble nanoparticles may be capable of rapid translocation into the circulation, with the potential for direct effects on cardiovascular integrity[101-103]. Experimental studies investigating the traslocation of inhaled UFPs into the blood circulation showed in hamsters the rapid clearance of instilled albumin nanoparticles from the lungs to the bloodstream (25-30% in 5 minutes)[101]; in humans, after inhaling ^{99m}Tc-labeled carbon nanoparticles, it could be observed the rapid appearance of the radioactive label in the blood followed by the significant accumulation in the liver[102].

The exact mechanism for this translocation remains to be established. UFPs could be involved in a transcytosis across epithelia of the respiratory tract into the interstitium and then they gain access to the blood circulation directly or *via* lymphatics. UFPs could also be cleared in the alveolar region by alveolar macrophages, through phagocytosis of deposited particles followed by gradual movement of the macrophages with internalized particles toward the mucociliary system. However due to difference in primary particles size and to degree of particles aggregation, UFPs may escape phagocytosis, or the cascade of events leading to alveolar macrophage-mediated clearance may be more or less effective. The rapidity of lung clearance[101,102] makes it unlikely that phagocytosis by macrophages and/or transcytosis across epithelial and endothelial cells are exclusively responsible for particle-translocation to the blood[102], as there is experimental evidence suggesting the existence of functional pores in the alveolar-blood barrier[103], through which UFPs may go directly in the blood, similarly to lung epithelial specific proteins[104]. Alternatively, a slower active transfer of particles from the lung into the circulation could explain a recent finding that the majority of ^{99m}Tc-labeled carbon nanoparticles remains within the lung up to 6 h after inhalation in humans[105]; in this case the traslocation may be intracellular due to phagocytosis of particulate in the lung alveolar space or interstitium by cells of the monocyte/macrophage lineage, which then enter the circulation[105]. The circulating particles may interact with vascular endothelium/atherosclerotic lesions, causing local oxidative stress that could destabilize plaques, setting off a chain reaction (rupture, thrombosis) with resultant acute cardiovascular events (acute coronary syndrome and stroke)[102,106]. Furthermore, particles may interact with circulating coagulation factors to promote thrombogenesis[106,107]. The UFPs/NPs could also have effects on cardiac physiology if they act directly or perhaps as a result of a local inflammatory response, on nerve endings in the walls of the airways throughout the respiratory system. Activation of such receptors initiates changes in the autonomic control of the heart and, thus, changes in the heart's rhythm (e.g. fatal arrhythmias)[76,77,79,108]. Environmental combustion-derived nanoparticulate, as a carrier of soluble organic compounds from unburned hydrocarbon fuels[109] and oxidized transition metals[109], may well exert an important influence on the cardiovascular system. They contain a high content of redox-cycling organic chemicals that not only could be released deep into the lungs but also could even spill over into the systemic circulation[109,110].

Potential other Target Tissues Toxicity

As explained previously, once deposited deeply into the lung, UFPs – in contrast to larger-sized particles – appear to access to the blood circulation by different transfer routes and mechanisms, resulting in distribution throughout the body. The liver is the major distribution site via uptake by Kupffer cells, followed by the spleen and bone marrow as other organs of the reticulo-endothelial system[111]. Through an innovative electron microscopy technique, the presence of nano-sized inorganic, neither biodegradable nor biocompatible particles were found in thrombi and fibrotic tissue taken from explanted vena cava filters in patients with blood coagulation disorders and recurrent pulmonary embolism[112,113]. UFPs did not belong to the metal the device was made of, probably deriving from pollutant sources, as the chemistry of these particles was different and varied, and unusual compounds containing non-biocompatible elements like bismuth, lead, tungsten were detected. They frequently activated immunological reactions typical of a foreign body. The interaction between these UFPs traveling in the blood stream and the blood itself might leads to suspect that the formation of the thrombus can originate from these inorganic and inert nanosized particles that act as triggering factors of the blood coagulation[112,113].

Once accessed the blood circulation, UFPs are so translocated to other organs including the liver, the spleen, the kidneys, the heart and the brain, where they may be deposited[114]. There is the potential for neurodegenerative consequence of particle entry to the brain. Histological evidence of neurodegeneration has been reported in both canine and human brains exposed to high ambient PM levels, suggesting the potential for neurotoxic consequences of PM entry[114]. PM mediated damage may be caused by the oxidative stress pathway. Thus, oxidative stress due to nutrition, age, genetics among others may increase the susceptibility for neurodegenerative diseases[114]. The relationship between PM exposure and central nervous system (CNS) degeneration can also be detected under controlled experimental conditions[114]. Transgenic mice (Apo E -/-), known to have high base line levels of oxidative stress, were exposed by inhalation to well characterized, concentrated ambient air pollution. Morphometric analysis of the CNS indicated unequivocally that the brain is a critical target for PM exposure and implicated oxidative stress as a predisposing factor that links PM exposure and susceptibility to neurodegeneration[114].

Recent experimental evidences in animals indicate traslocation of UFPs to ganglionic and central nervous system structures trough a mechanism that involves their uptake by sensory nerve endings embedded in airway epithelia, followed by axonal transport[115].

In experimental animal models translocation of UFPs to the central nervous system has also been described trough a mechanism involving the olfactory bulbs and the olfactory nerve, as the close proximity of nasal olfactory mucosa and olfactory bulb requires only a short distance to be covered by neuronal transport[116,117]. Collectively, these studies point out that under conditions of environmental and occupational exposures of humans to airborne UFPs, the airway sensory nerve and the olfactory nerve pathways should also be considered a portal of entry of UFPs to the central nervous system, but confirmatory studies are necessary.

Indirect evidence for movement of UFPs along axons and dendrites in humans is provided by knowledge accumulated by virologists who have long understood the movement of human meningitis virus through olfactory and trigeminal neurons and, similarly, herpes virus movement up and down the trigeminal neuron to trigger outbreaks of herpes cold sores in humans[118,119].

In the context of potential central nervous system effects of air pollution UFPs, a recent study with exposures of mice to concentrated ambient fine particles and UFPs found significant increases of tumor necrosis factor-α (TNF-α) or decreases in dopaminergic neurons, supporting the hypothesis of ambient particulates causing neuro-degenerative disease[120]. An other study described significant inflammatory or neurodegenerative changes in the olfactory mucosa, olfactory bulb, and cortical and subcortical brain structures in dogs from a particulates heavily polluted area in Mexico City, whereas these changes were not seen in dogs from a less-polluted rural control city[121]. However, whether direct effects of airborne UFPs were the cause of these central nervous system consequences remains to be determined. Moreover, evidences of neurologic pathologies due to the presence of UFPs in the human CNS are to date still lacking.

Discussion

Epidemiological studies indicate associations between exposure to ambient UFPs and adverse

health effects. The lung is the primary target of UFPs, but also their portal of entry into the human body with the cardiovascular system emerging as the final most sensitive target. Cardiovascular detrimental consequences due to UFPs exposure have been observed in epidemiological studies, and could likely be explained by translocation of UFPs from the respiratory epithelium towards circulation and subsequent toxicity to vascular endothelium; alteration of blood coagulation; triggering of autonomic nervous system reflexes eventually altering the cardiac frequency and function. Respiratory and cardiovascular tissues are highly vulnerable to UFPs exposure, which should be recognized as a cardiopulmonary hazard. Respiratory and cardiovascular disease risk factors, endemic in industrialized societies, are likely influenced by environmental exposure to harmful chemicals and pollutants.

Neurological consequences of UFPs have been showed in experimental animal models, but little is known in humans. The environmental context within which a pathophysiological process takes place should be studied as closely and rigorously as the biochemical mechanism of the pathological process. At present, most investigators address only disease biochemical mechanisms that contribute to disease development and individual susceptibility genes, while genes/environment interaction are considered less relevantly in the disease generating pathological process. The environment could induce complex genetic alterations due to the plasticity of the genome which might react to thousands of pollutants[122]. These alterations could persist in succeeding generations through epigenetic and genetic changes[122]. Experimental data show that male mice exposed to ambient air near an urban industrial site in Canada[123] showed a 1.5- to 2-fold increase in germline mutation rate and that removal of particulate air pollution reduced heritable mutation rates at repetitive DNA loci pollutants[124]. Although pollutant-induced inheritable changes have not been demonstrated in humans, increased episodic air pollution have been linked to increased DNA fragmentation in human sperm[125]

UFPs represent an area of toxicology of emerging concern. A multidisciplinary approach including atmospheric scientist, nanomaterial engineers, epidemiologists, clinicians and toxicologists is necessary to investigate UFPs sources, generation, physicochemical characteristics and potential harmful effects following their inhalation. A new concept of environmental medicine would help in understanding not only the environmental mechanisms of disease, but also in developing specific preventive or therapeutic strategies for minimizing the dangerous influence of pollution on health.

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