

Lung injury after cigarette smoking is particle related

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Abstract: The specific component responsible and the mechanistic pathway for increased human morbidity and mortality after cigarette smoking are yet to be delineated. We propose that 1) injury and disease following cigarette smoking are associated with exposure to and retention of particles produced during smoking and 2) the biological effects of particles associated with cigarette smoking share a single mechanism of injury with all particles. Smoking one cigarette exposes the human respiratory tract to between 15,000 and 40,000 μg particulate matter; this is a carbonaceous product of an incomplete combustion. There are numerous human exposures to other particles, and these vary widely in composition, absolute magnitude, and size of the particle. Individuals exposed to all these particles share a common clinical presentation with a loss of pulmonary function, increased bronchial hyperresponsiveness, pathologic changes of emphysema and fibrosis, and comorbidities, including cardiovascular disease, cerebrovascular disease, peripheral vascular disease, and cancers. Mechanistically, all particle exposures produce an oxidative stress, which is associated with a series of reactions, including an activation of kinase cascades and transcription factors, release of inflammatory mediators, and apoptosis. If disease associated with cigarette smoking is recognized to be particle related, then certain aspects of the clinical presentation can be predicted; this would include worsening of pulmonary function and progression of pathological changes and comorbidity (eg, emphysema and carcinogenesis) after smoking cessation since the particle is retained in the lung and the exposure continues.

Keywords: particulate matter, smoking, oxidants, oxidative stress, air pollution

Introduction

Smoking is one of the ten greatest contributors to global death and disease¹ and is the single most important risk factor for chronic obstructive pulmonary disease (COPD), cardiovascular disease, cerebrovascular disease, peripheral vascular disease, and numerous cancers in the United States.² The specific component responsible and the mechanistic pathway for increased human morbidity and mortality after cigarette smoking are yet to be delineated. Cigarette smoking is a particle-related exposure. While obvious disparities exist between cigarette smoking and exposures to other particles, there are many similarities in the physiologic changes, pathology, and comorbidities. We propose that 1) injury and disease following cigarette smoking are associated with exposure and retention of particles produced during smoking and 2) the biological effects of particles associated with cigarette smoking share a single mechanism of injury with all particles.

Human exposures to particles

In a burning cigarette, temperatures in the combustion zone (800°C–950°C) result in a complete pyrolysis of tobacco.³ Immediately downstream, a rapid drop in temperature

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(to 200°C–600°C) and a lack of oxygen allow for incomplete combustion of tobacco. Subsequently, a complex aerosol is generated during smoking, which includes condensed liquid droplets (the particulate fraction or tar) suspended in a mixture of volatile and semivolatile compounds and combustion gases (the gas fraction). Smoking one cigarette exposes the human respiratory tract to between 15,000 and 40,000 µg particulate matter (PM).⁴ The composition of cigarette smoke PM is comparable to that of other particles generated through an incomplete combustion of carbonaceous material, and this includes a heterogeneous, amorphous, organic material.^{5–7}

Human exposures to other particles vary in composition, absolute magnitude, and size of the particle (Table 1). After cigarette smoking, the burning of biomass (defined as some combination of wood, charcoal, agricultural residues, and animal dung) is likely to be the PM source of greatest significance internationally. More than 2 billion people in the world use biomass as their main source of energy for domestic heating and cooking, and 80% of total global exposure to PM occurs indoors in developing nations.

Particle-related lung injury

Individuals exposed to all these different particles share a common clinical presentation. Depending on the composition, magnitude, and duration of the particle exposure, there can be 1) loss of pulmonary function, 2) increased bronchial hyperresponsiveness, 3) pathological alterations of emphysema and fibrosis, 4) hemorheological changes, and 5) comorbidities, including cardiovascular disease, cerebrovascular disease, peripheral vascular disease, and cancers.

Loss of pulmonary function

Smoking cigarettes decreases all indices of lung function but particularly affects flows.⁸ On an average, moderate-to-heavy male smokers have a 15 mL/year larger decline in forced expiratory volume in 1 sec relative to nonsmokers.⁹ The greater the number of cigarettes smoked (ie, pack years), the higher the rate of decline in lung function.⁹ The extreme loss of function after cigarette smoking can result in COPD, a major cause of morbidity and mortality throughout the world. COPD, a disease state characterized by airflow limitation that is not fully reversible, is currently the fourth leading cause of death in the world, and further increase in the prevalence and mortality of the disease is predicted in the coming decades. Internationally, the prevalence of COPD is highest in countries where cigarette smoking is common.¹⁰

Other particle exposures are similarly associated with loss in pulmonary function and COPD. Environmental tobacco smoke (ETS),^{11–13} woodstove emissions,¹⁴ use of gas stoves, burning of biomass other than wood,^{15–19} and air pollution particles²⁰ decrease indices of pulmonary function. COPD has been observed among nonsmoking individuals exposed to both open fires/burning of biomass^{21,22} and occupational dusts, including coal and mineral oxide particles.²³

Bronchial hyperreactivity

Cigarette smoking^{24,25} and ETS exposure^{26,27} elevate bronchial hyperresponsiveness. There is a dose-dependent relationship between the number of cigarettes smoked and the degree of hyperresponsiveness.²⁸ Particles other than those in cigarette smoke similarly affect bronchial hyperresponsiveness. Diesel exposure has been associated with

Table 1 Particle-related exposures associated with human lung injury

Particle source	Composition of particle	Magnitude of exposure	Particle size
Cigarette smoking	Carbonaceous combustion product	15,000–40,000 µg/cigarette	Fine and ultrafine
Environmental tobacco smoke ^{137–139}	Carbonaceous combustion product	≤1000 µg/m ³	Fine and ultrafine
Forest fires ¹⁴⁰	Carbonaceous combustion product	≤1000 µg/m ³ but variable	Fine and ultrafine
Wood-burning stove ^{141–143}	Carbonaceous combustion product	≤1200 µg/m ³	Fine and ultrafine
Gas stove ^{144,145}	Carbonaceous combustion product	≤1380 µg/m ³	Fine and ultrafine
Diesel exhaust ^{146,147}	Carbonaceous combustion product	≤10 µg/m ³ in ambient air <1000 µg/m ³ in mines	Ultrafine
Burning of biomass ^{145,148–150}	Carbonaceous combustion product	≤10,000 µg/m ³ but variable	Coarse, fine, and ultrafine
Air pollution ¹⁵¹	Variable	≤50 µg/m ³ nationally ≤500 µg/m ³ internationally	Coarse, fine, and ultrafine
Coal mining	Carbonaceous	≤2000 µg/m ³ nationally	Coarse and fine
Mining of minerals	Inorganic (eg, silica and silicates)	≤1000 µg/m ³ for silica ≤5000 µg/m ³ for nuisance dust	Coarse and fine

comparable changes in bronchial hyperresponsiveness.²⁹ The response to methacholine also increases following exposure of firefighters.^{30–32} Occupational exposure to dust can increase airway reactivity, including both coal dust^{24,33} and mineral oxide.³⁴ This relationship between particle exposure and bronchial responsiveness is widely recognized, and a challenge inhalation with particles has been proposed as an alternative to methacholine testing.^{35,36}

Lung histopathology

Cigarette smoking has been associated with an acute influx of neutrophils into the lower respiratory tract.³⁷ This is comparable to other particle-associated injuries, including exposures to ambient air pollution particles and diesel exhaust.^{38,39}

The two chronic pathologic processes noted on microscopic inspection of the lungs from individuals exposed to particles are emphysema and fibrosis. Emphysema is most frequently caused by cigarette smoking, but is also observed after other particle exposures, including burning of biomass,⁴⁰ mineral oxide,^{23,41,42} and coal dust.^{43–47} Histologically, emphysema, following all these exposures, including cigarette smoking, occurs immediately adjacent to the retained particle.^{48–51} In one animal study, the emphysema severity was dependent on the concentration of cigarette smoke total PM.⁵² Mucous cell hyperplasia, hypertrophy, and inflammatory cell infiltrates were present in the epithelium of large airways of cigarette smoke-exposed mouse lungs. Further, allowing the mice to recover from cigarette smoke exposure was not associated with reversal of emphysema, and cigarette smoke-induced pulmonary inflammation also persisted.

Fibrosis can also be observed following exposures to numerous different particle exposures. Increased collagen is frequently observed in the lungs of cigarette smokers,^{53–55} and irregular opacities reflecting this fibrosis can be observed on their chest X-rays comparable to those in pneumoconioses.^{23,56–58} Collagen deposition and fibrosis in the human lung have been described following exposure to ambient air pollution particles,⁵⁹ environmental exposure to crustal particles (eg, windstorms),^{60,61} and inhalation of emission source particles.⁶² This fibrogenic property of particles is exploited therapeutically with the instillation of gram quantities of a mineral oxide (ie, talc) particle into the pleural space to provide sclerosis.⁶³

Hemorheological changes

Cigarette smoking leads to a rise in hematocrit, increased total white cell count, and modified leukocyte function.

Elevations in the plasma concentrations of fibrinogen are also associated with smoking;^{64,65} a dose–response relationship between smoking and the plasma fibrinogen level has been described.⁶⁶ Following smoking cessation, plasma fibrinogen will drop immediately but takes 5 years to return to normal.⁶⁷ Abnormalities in platelet function can similarly occur with smoking with an increase in platelet aggregation occurring as rapidly as 10 min after smoking a cigarette.^{68,69}

Other particle exposures elicit comparable changes in blood components. ETS exposure can be associated with platelet aggregation.⁷⁰ Ambient air pollution particles effect several changes in the peripheral blood, including decreases in red cell number,⁷¹ elevations in white blood cell counts,⁷¹ and increases in C-reactive protein,⁷¹ fibrinogen,^{38,71,72} and blood viscosity;^{71,73} the last two potentially contribute to the association of ambient PM with thrombotic events.⁷⁴ Other particles have comparable effects on hemorheologic indices.^{75,76}

Comorbidities

Cigarette smoking is the major risk factor in many industrialized societies for cardiovascular disease and increases the prevalence of coronary artery disease,^{77,78} cerebrovascular disease,⁷⁹ and peripheral vascular disease.⁸⁰ Convincing evidence also links ETS exposure to both cardiac morbidity and mortality and peripheral vascular disease.⁸¹ Forest firefighting⁸² and diesel exhaust⁸³ similarly elevate the rate of cardiovascular disease. The inhalation of ambient air pollution PM can increase the incidence of myocardial infarction,⁸⁴ hospital admission for cardiovascular diseases,⁸⁵ and the rate of arrhythmias.⁸⁶ Finally, exposures to mineral oxide and coal dust can be associated with an increased risk for cardiovascular disease.^{87,88}

There are elevations in the incidence of cancer with either cigarette smoking⁸⁹ or exposure to ETS.^{90,91} There is also concern for an induction of neoplasms by other particle-associated injuries, including that induced by diesel exhaust,⁹² forest fire fighting,⁹³ burning of biomass other than wood,⁹⁴ the use of wood-burning stoves,⁹⁵ and occupational exposures to silica.⁹⁶ Recent investigation has similarly suggested a carcinogenicity of ambient air pollution particles.⁹⁷

Mechanism of injury following particle exposures

Shared characteristics of the physiologic response, pathology, and comorbidities between PM included in cigarette smoke and other particles suggest a common mechanism of biological effect. All particle exposures produce an oxidative stress.

A generation of reactive oxygen species results either directly from some component of the particle supporting an inappropriate electron transfer or from an interaction of the PM with cell proteins (eg, electron transport complexes in the mitochondria). Oxidative stress is accepted as the initial step in the biological effect after cigarette smoking⁹⁸ and all other particle exposures.⁹⁹

Oxidants generated by particle exposures can cause sequential changes culminating in tissue injury (Figure 1). Among the early cell targets of oxidative stress are kinase cascades. Mitogen-activated protein (MAP) kinases (p38 MAP kinase family, the extracellular signal-regulated kinase (ERK) family, and the c-Jun NH₂-terminal kinase (JNK) family) are widely expressed serine–threonine kinases which mediate regulatory signals in the cell. The activation of specific MAP kinase signaling cascades is required for induction of various cellular responses, including phosphorylation of transcription factors (eg, NF-E2-related factor 2 (Nrf2), nuclear transcription factor-kappaB (NF-κB), and activator protein-1 (AP-1)) and transcriptional regulation, nuclear chromatin remodeling and gene induction, cytokine production, as well as regulation of apoptosis and cell-cycle progression.¹⁰⁰ Exposure to cigarette smoke leads to activation of MAP kinases and pro-inflammatory transcription factors (Nrf2, NF-κB, and AP-1), and this is considered to be a key mechanistic event leading to cell differentiation, release of inflammatory mediators, and inflammatory

injury in the lungs.^{101–107} Regarding one transcription factor, macrophage exposure to cigarette smoke induced nuclear accumulation of Nrf2 and activated the transcription of Nrf2 target genes.¹⁰⁸ This suggests that Nrf2 in macrophages may participate in the human response to cigarette smoke exposure. Basal Nrf2 mRNA levels and Nrf2 target gene expressions were significantly lower in alveolar macrophages obtained from 1) older current smokers relative to and from lifelong nonsmokers and 2) patients with COPD relative to nonsmokers and former smokers without COPD. The same cascade of reactions (Figure 1) appears to also participate in cell apoptosis after cigarette smoke exposure.^{109–114}

The pathway of inflammation and apoptosis following exposure to other particles is indistinguishable from that after cigarette smoke exposure (Figure 1). Numerous PM exposures activate the same kinases and pro-inflammatory transcription factors observed with cigarette smoke.^{115–118} Comparable to cigarette smoke, the same particles subsequently affect a release of inflammatory and apoptotic mediators.^{119–124}

Activation of kinase cascades and transcription factors following particle exposure can also effect an inflammatory and apoptotic response in extrapulmonary sites. Mainstream cigarette smoke exposure is associated with activation of p38 and ERK1/2 MAP kinases.¹²⁵ Ambient air pollution particles similarly induce reactive oxygen species generation in human endothelial cells, resulting in cell barrier disruption via p38 MAP kinase–dependent pathways.^{126,127} These findings support one common pathway for biological effect of all particles in all tissues.

Conclusions

Particle-related biological effects continue to be defined. Investigation has demonstrated comparable effects of cigarette smoke and other particle-related exposures. A shared mechanism of biological effect between cigarette smoking and other particle exposures would further understanding of human disease. If disease associated with cigarette smoking is recognized to be particle related, then certain aspects of the clinical presentation can be predicted. For example, worsening of pulmonary function and progression of pathological changes after smoking cessation is predicted since the particle continues to be sequestered in the lung, and biological effect corresponds to such persistence.^{128–130} Finally, a shared pathway of biological effect predicts that genetic predisposition to one particle-related injury may also influence another (eg, polymorphisms in glutathione transferase will function as a risk factor in injury after cigarette smoking and exposure

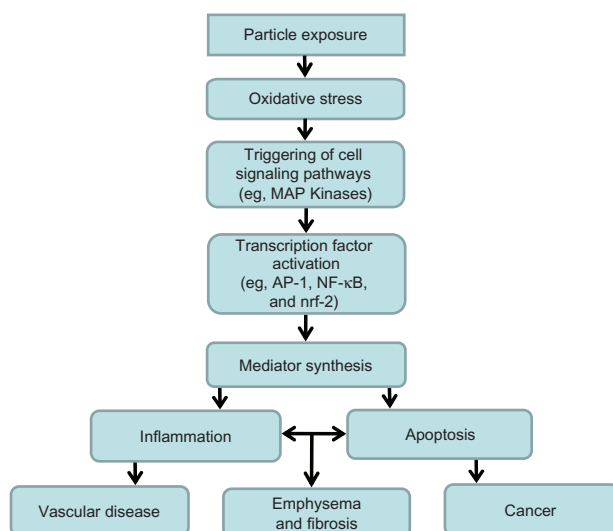


Figure 1 Mechanism of biological effect following particle exposure. Particles effect an oxidative stress, which prompts a series of reactions by the host, including activation of cell signaling pathways and transcription factors and inflammatory mediator release. This culminates in inflammation and apoptosis which, if prolonged or misregulated, can produce emphysema, fibrosis, vascular disease, and cancer.

Abbreviations: MAP, mitogen-activated protein; AP-1, activator protein-1; NF-κB, nuclear transcription factor-kappaB; Nrf2, NF-E2-related factor 2.

to air pollution particles).^{131,132} Those genetic factors which are demonstrated to participate in lung injury after either cigarette smoking or other specific disease following particle exposure should be examined for a contribution in any of the particle-related diseases.^{133–136}

Disclaimer

This report has been reviewed by the National Health and Environmental Effects Research Laboratory, United States Environmental Protection Agency, and approved for publication. Approval does not signify that the contents necessarily reflect the views and policies of the agency nor does mention of trade names or commercial products constitute endorsement or recommendation for use.

Disclosure

The authors report no conflicts of interest in this work.

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