Pathophysiology 23 (2016) 285–293

Contents lists available at ScienceDirect

Pathophysiology

journal homepage: www.elsevier.com/locate/pathophys

Review

Biochemical and physiological effects from exhaust emissions. A review of the relevant literature

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ARTICLE INFO

Article history:
Received 27 June 2016
Accepted 20 October 2016

Keywords:
Exhaust
Emissions
Biochemistry
Cell responses
Molecular biology
Disease mechanisms

ABSTRACT

Exhaust emissions are to date ranked among the most frequent causes of premature deaths worldwide. The combustion of fuels such as diesel, gasoline, and bio-blends provokes a series of pathophysiological responses in exposed subjects, which are associated with biochemical and immunological triggering. It is critical to understand these mechanisms, which are directly related to the levels of aerosol, liquid and gaseous components in fuel exhaust (*e.g.* nanoparticles, particulate matter, volatile compounds), so to cast attention on their toxicity and gradually minimize their use. This review reports findings in the recent literature concerning the biochemical and cellular pathways triggered during intoxication by exhaust emissions, and links these findings to pathophysiological responses such as inflammation and vasoconstriction. This study provides critical *in vitro* and *in vivo* data for the reduction of emissions in urban centers, with an emphasis on the prevention of exposure of groups such as children, the elderly, and other affected groups, and shows how the exposure to exhaust emissions induces mechanisms of pathogenesis related to cardiopulmonary pathologies and long-term diseases such as asthma, allergies, and cancer. This review summarizes the cellular and physiological responses of humans to exhaust emissions in a comprehensive fashion, and is important for legislative developments in fuel politics.

Contents

1. Introduction

Exhaust emissions are ranked as one of the prime causes of death worldwide, and are reported to induce strokes, heart arrhythmia, heart infarct, and cardiac arrest [1,2]. The cause of many of these conditions is directly related to the properties of the toxic components of air pollution; for instance, $PM_{2.5}$ and PM_{10} (particulate matter with diameter less than 2.5 μm and 10 μm, respectively) have a strong impact on cardiac function [2,3], while ultra-small nanoparticles tend to affect lung function by causing asthma, chronic bronchitis, and pulmonary disorders [4–7]. The effects from emissions of fuel combustion are also closely related to the chemical characteristics of the pollution components, and as these compounds are continuously changing with the development of

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http://dx.doi.org/10.1016/j.pathophys.2016.10.002
0928-4680/

new and alternative fuel variants, such as bio-blends with gasoline or diesel [8], it is critical that new assessments of air pollution data be reviewed. Recent reviews show a close relationship between ultrafine particles, their chemical properties, and detrimental physiological responses in individuals exposed to air pollution [8–16]. However, the current state of knowledge does not contain sufficient information about the cellular mechanisms that occur during exposure to air pollution of various types. While knowledge of the chemical and mutagenic properties of pollution components, such as polycyclic aromatic hydrocarbons (PAH), is fairly extensive to date [17–26], information concerning the cellular factors involved in cellular reactions to pollution is scarce. Concomitantly, the cellular and molecular biology events taking place during intoxication provide a medical basis for arguments in favour of developing better fuels with less toxic emission compounds. The development of novel fuels should therefore be attuned to the molecular biology behind the pathology induced by exhaust emissions, and be used by health legislators to prevent introduction and continuous use of forms of fuel hazardous to health, whether these are conventional fuels or alternative fuels. Therefore, the implementation of novel fuel sources requires a careful consideration of the molecular biology mechanisms at the DNA and proteomic levels, both to understand the responses from exposed individuals, and to track and predict the toxic potential of exhaust emission fumes and particles. This review evaluates the studies done over the last 30 years on air pollution resulting from the combustion of gasoline, diesel, and alternative blends, such as bioethanol and biodiesel. DNA-adduct formation, cytotoxic events, cell-growth altering mechanisms, and other pathological cell responses are examples of this pivotal evaluation of the mutagenic and genotoxic effects imposed on the cells by exhaust emissions. The review is divided into classes of proteins and complexes and their reported levels of expression to air pollution.

1.1. Cadherin related responses to exhaust emissions

The effects of particulate matter on the genomic activity of cadherin genes have been recently published [27]. The study encompasses a large cohort of more than nine thousand individuals, who were screened over a period of 11 years for genomic activity upon exposure to PM_{10}. The cohort was subdivided into sections in several geographical areas, which were continuously screened for PM_{10} concentrations from outdoor air. The sampling of individuals included DNA sampling and blood tests to identify increments or changes in the population of cellular and circulating factors in the blood of the individuals exposed to PM_{10}. The study, which is the first of its kind performed on such an extensive scale, showed that PM_{10} levels triggered a particular genomic location in the test subjects during exposure. The associated locus, the CDH13 SNP cluster, encodes for a series of proteins, one of which is cadherin 13 [27]. Cadherin 13 is expressed in the lungs upon PM_{10} exposure and may have a direct role protecting the extracellular matrix and tissue surface from the chemical reactions taking place between the PM_{10} components and the lung tissue, thus maintaining healthy lung function during exposure. Cadherin 13 is expressed on the surface of the cell, and differs from other integrated proteins in that it can be released after hydrolysis of its glycosylphosphatidylinositol anchor. At its release into the blood, the protein carries out important functions. Studies show that cadherin 13 is downregulated in various types of cancers [28], and has been reported to be a tumor suppressor with a potential for use in diagnostic medicine [29]. The expression of cadherin 13 in subjects exposed to PM_{10} could be a mechanism against generic oxidative effects, mechanisms that potentially contribute to tumor development [30]. Cadherin 13 expression is therefore potentially related to action taken by the lung tissue to maintain respiratory health

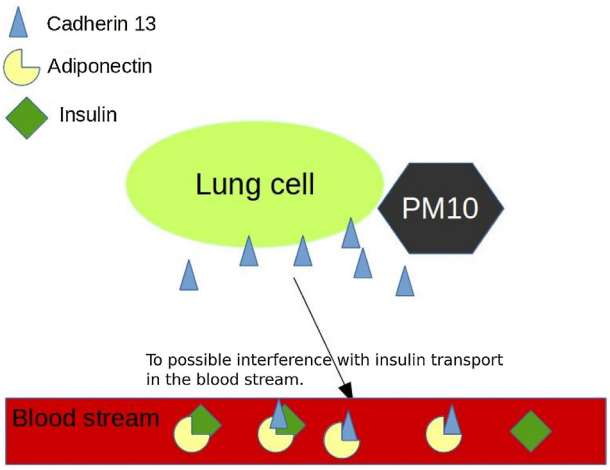

Fig. 1. The Cadherin-Adiponectin mechanisms during PM_{10} intoxication. The chart shows how lung cells release cadherin 13 proteins from the cell surface during PM_{10} intoxication and how this is directly linked with adiponectin function. Once cadherin 13 is transferred into the blood during PM_{10} intoxication, it can affect adiponectin function by possibly interfering with insulin transport.

through its interaction with a second protein, adiponectin [27]. This secondary protein, adiponectin, is sequestered in the blood by cadherin 13, and carries out several functions, one of which is to regulate inflammation [31,32]. Adiponectin is a hormone-derived protein from adipocytes (fat cells), and has recently been found to decrease insulin resistance [33], thus reducing the risk of diabetes [34]. Given the sensitive mechanism involved, it is feasible that during prolonged exposure to PM_{10}, higher levels of cadherin 13 are triggered, resulting in reduced levels of free adiponectin (Fig. 1). This affects insulin resistance, as adiponectin is crucial to its reduction [33]. The relationship among the role of adiponectin and insulin levels, pulmonary function, and the tumor-suppressing role of cadherin 13 therefore demonstrates an interesting network of interactions. This network suggests that long-term exposure to PM_{10} may not only reduce lung function maintenance, but may also interfere with insulin metabolism, as adiponectin plays a central role in regulating insulin levels [33,34]. This is supported by evidence from other studies on reactions to smoke of other kinds, particularly cigarette smoke. In a study by Wang et al., the response to inhalation of cigarette smoke shows induction of changes in levels of cadhedrins in the blood [35]. More recently, Koning et al. have reported similar findings in mouse models [36]. Interestingly, altered levels of cadherins in the pulmonary system also result from the inhalation of ozone in mice, which suggests that the trigger for cadherin-level disturbances may be ROS (reactive oxygen species) or oxygen-rich reactive molecules, since combusted cigarette smoke and exhaust emissions contain few active oxygen species, but rather mostly oxidized nitrogen and carbon species [8]. The unequivocal effect from these disturbances also leads to the expression of cytokines, which mediate the vascular permeability of capillary endothelium, as one of several functions as described in the following chapter [37].

1.2. Cytokines and interleukins

Cytokines and interleukins are anti-oxidative cellular factors expressed by the cell during exposure to air particulates and particles from exhaust emissions, including NO_x species. A recent study from Germany [38] reports the responsiveness of pro-inflammatory cytokines to NO_2, NO_x, PM_{10}, and $PM_{2.5}$ in asthmatic and non-asthmatic children. The results from this study show that NO_2 induces a doubling of pro-inflammatory factor interleukin-6 for every increase of 2.68 $\mu g/m^3$ NO_2 in the outdoor air. Expres-