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Diesel effects on human health: a question of stress?

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IN THIS ISSUE in one of the current articles in focus (Ref. 3, see p. L724 in this issue), Pourazar et al. provide the first human in vivo evidence to support the concept that air pollutants target the airways through induction of oxidative stress (3). The last decade has seen a deluge of reports illustrating the health effects of air pollution (1). The most prominent effect seems to be on the respiratory system, and exposure to either gaseous pollutants (such as ozone or nitrogen dioxide) or particulate pollutants (such as diesel) can lead to exacerbation of asthma, bronchitis, wheezing, or to slowing of children's lung development. In addition, it can interact with allergen to worsen allergic symptoms, increase allergic antibody production, and augment allergic sensitization.

The mechanisms by which these adverse outcomes occur are a focus of intense investigation by many groups worldwide. Despite the distinct nature of the different components of air pollution, it seems that both particulate and gaseous pollutants alike share the ability to initiate and heighten cellular inflammation in upper and lower airways. In both human and animal models, increases in airway inflammatory cells, such as neutrophils, macrophages, and lymphocytes, are observed after exposure to diesel particles, ozone, SO_2, or NO_2. Accompanying and presumably causing these cellular responses is an increase in proinflammatory cytokines and chemokines.

Of the pollutants studied, diesel exhaust and its constituent particles have recently received the most attention (4). The rapid rise in diesel truck traffic in the United States and automobile traffic worldwide and worries over exposure of children to diesel fumes from school buses have fuelled public health concern. That diesel exhaust particles (DEP) are capable of profound proinflammatory and proallergenic effects is firmly established. In vitro studies have highlighted the puzzling features of DEP to target multiple cell types directly. Thus, cytokine release from epithelial cells, monocytes, neutrophils, lymphocytes, and mast cells stimulated with DEP or the chemicals they contain have all been reported. What mechanism could be responsible for targeting this broad spectrum of cells?

A wide range of studies has demonstrated that several components of DEP can induce oxidative effects on airway cells (6). Moreover, antioxidants can block DEP effects in animal and in vitro models. Almost since the cytokine's discovery, it has been known that oxidant stress is an important regulator of IL-8 gene expression, and it has been proposed that recruitment of neutrophils to sites of inflammation is accomplished by generation of reactive oxygen species (ROS)-initiated IL-8 production. Other cytokines, such as TNF-α and IL-6, are also known to be under similar control. It has, therefore, been suspected that DEP activate redox-sensitive transcription factors such as NF-κB and activator protein (AP)-1, which regulate expression of many proinflammatory cytokines. DEP-induced ROS would initiate intracellular signaling and transcriptional activation of cytokine and chemokine genes, resulting in a heightened inflammatory response. Until now, evidence for this hypothesis has been mainly from in vitro studies that show, for example, that JNK and MAPK can be activated by chemicals extracted from DEP. Pourazar et al. (3) take the mechanistic search to human subjects and rather convincingly demonstrate that NF-κB, AP-1, JNK, and p38 are strongly activated in bronchial cells from healthy human subjects exposed to diesel exhaust compared with exposure to filtered air. This translational study fills a gap and provides the necessary evidence to confirm that proposed oxidative stress pathways seen in in vitro/animal studies are in fact relevant to the health of human patients.

It is important to recognize that this study was performed with healthy human subjects not affected by respiratory conditions such as asthma or chronic obstructive pulmonary disease. Mechanistic studies similar to this one, but examining "vulnerable" patients with respiratory disease, are likely to be informative and necessary to fully understand the effects of DEP on human respiratory health. Although such investigations will need to be performed cautiously and ethically, previous human studies have suggested that healthy and asthmatic patients differ in their response to particulate air pollution, at least by functional measurements (5). Future studies may show whether there are differences in activation levels in healthy individuals compared with those with chronic respiratory conditions or with atopy.

This study raises other important questions. First, the lack of epithelial IL-13 and Gro-α expression is unexpected, as previous work suggests these are strongly linked to NF-κB activation. Presumably, other regulatory mechanisms are at work, but these remain to be defined. Second, it will be interesting to see whether activation of these same factors occur upon exposure to other pollutants, such as ozone, given the similar health outcomes observed. Last, responses to diesel or air are quite variable between individuals in this study. The data demonstrate that some individuals have very robust NF-κB activation to DEP, whereas others have relatively modest responses. When individuals were compared, some subjects had lower p38/c-jun activation levels with DEP exposure than others had with exposure to filtered air. This suggests a significant variability in the intrinsic susceptibility of individuals to the oxidative effects of DEP. Previous work suggests that cytoprotective phase II enzymes such as glutathione-*S*-transferase (GST) M1 and GSTP1 are likely important determinants in the inflammatory response to respiratory diesel exposure (2). Individual responses to DEP over time as well as genotyping data would be an informative extension of this work. Ultimately,

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identifying these potential protective factors will be an important step in developing and testing interventions to reduce the harmful respiratory effects of pollutant-induced oxidative stress.

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