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Review Article

Investigating the Potential for Interaction between the Components of PM_{10}

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Abstract

The adverse health effects of elevated exposures to PM_{10} (particulate matter collected through a size selective inlet with an efficiency of 50% for particles with an aerodynamic diameter of 10 μm) in relation to morbidity and mortality, especially in susceptible individuals, are now well recognised. PM_{10} consists of a variable cocktail of components differing in chemical composition and size. Epidemiological and toxicological data suggest that transition metals and ultrafine particles are both able to drive the cellular and molecular changes that underlie PM_{10}-induced inflammation and so worsen disease status. Toxicological evidence also suggest roles for the biological components of PM_{10} including volatile organic compounds (VOC's), allergens and bacterial-derived endotoxin. Many of these components, in particular transition metals, ultrafine particles, endotoxin and VOC's induce a cellular oxidative stress which initiates an intracellular signaling cascade involving the activation of phosphatase and kinase enzymes as well as transcription factors such as nuclear factor kappa B. Activation of these signaling mechanisms results in an increase in the expression of pro-inflammatory mediators, and hence enhanced inflammation. Given that many of the components of PM_{10} stimulate similar or even identical intracellular signaling pathways, it is conceivable that this will result in synergistic or additive interactions so that the biological response induced by PM_{10} exposure is a response to the composition rather than the mass alone. A small number of studies suggest that synergistic interactions occur between ultrafine particles and transition metals, between particles and allergens, and between particles and VOC's. Elucidation of the consequences of interaction between the components of PM_{10} in relation to their biological activity implies huge consequences for the methods used to monitor and to legislate pollution exposure in the future, and may drive a move from mass based measurements to composition.

Key words: PM_{10}, ultrafine, metal, synergism, endotoxin

Introduction

Many toxicology studies have investigated the biological effects of either whole PM_{10} (particulate matter collected through a size selective inlet with an efficiency of 50% for particles with an aerodynamic diameter of 10 μm), or of individual PM_{10} components. To date, few studies have attempted to look for interactions between the components of PM_{10}. This review aims to highlight the components of PM_{10} suspected of being responsible for its health effects and then to suggest interactions between these components which might help to explain the adverse health effects associated with PM_{10} exposure in susceptible individuals.

Adverse health effect of increased PM_{10}

Despite the evolution of sophisticated physiological mechanisms to minimise the impact of inhaled particles by promoting their removal, a large number of epidemiological studies suggest that elevated levels of atmospheric PM_{10} results in increased adverse health effects in susceptible individuals. For example, PM_{10} pollution episodes have consistently been associated with increased mortality, resulting from cardiovascular and respiratory causes (Dockery and Pope 1994, Schwartz 1994). The increase in cardiovascular deaths has been suggested to result from an increase in the risk of blood clotting (Seaton et al. 1995). This hypothesis is supported by data obtained from the MONICA study in which there was a clear association between an air pollution episode in Ausburg in 1985 and an increase in plasma viscosity (Peters et al. 1997). This change was recently shown to be a result of an acute phase response (APR), as reanalysis of the same plasma samples revealed elevated C reactive protein (CRP) levels (Peters et al. 2001). The demonstration of an APR in individuals exposed to PM_{10} is important as there is a direct relation between the plasma levels of acute phase reactants such as fibrinogen and CRP, and sudden deaths for cardiovascular causes (Dhainaut et al. 2001, Yeun et al. 2000).

Epidemiological reports of the effects of PM_{10} on morbidity show that a number of endpoints are increased such as exacerbation of asthma (von Mutius 1998) and COPD (Brauer et al. 2001)

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Table 1 Classification of the components of PM_{10}

Classification	Description	
Particle Size	Coarse	2.5–10 μm diameter
	Fine	less than 2.5 μm diameter
	Ultrafine	less than 100 nm diameter
Primary and Secondary	Primary	remain in the form in which they were generated, e.g. diesel soot
	Secondary	arise as a result of atmospheric chemical reactions between pollutants e.g. ammonium sulfate
Organic and inorganic	Organic	derived from living sources e.g. spores and pollen
Indoor and outdoor	Indoor particles	dominated by indoor sources such as cigarette smoke and cooking fumes

as well as increased hospital admissions (Dockery and Pope 1994).

The components of PM_{10}

PM_{10} samples contain a wide range of particles, derived from a variety of sources and as a consequence can be classified in a number of ways (Table 1).

Particle size and ultrafine particles

Ferin et al. (1992) demonstrated that ultrafine particles made of low-toxicity materials such as titanium dioxide, were more inflammogenic in the rat lung after exposure by either instillation or inhalation, than larger, respirable particles of the same material. As a consequence of such observations Seaton et al. (1995) hypothesized that the ultrafine component of PM_{10} might be responsible for inducing pulmonary inflammation leading to the observed adverse health effects reported by the epidemiologists.

Subsequent toxicological studies have confirmed that ultrafine particles of different chemical compositions such as carbon black (Brown et al. 2000) and polystyrene beads (Brown et al. 2001) are in fact more inflammogenic than fine particles of the same chemical composition. Furthermore, these studies suggest that the ultrafine particles act by generating reactive oxygen species, leading to the induction of oxidative stress (Stone et al. 1998, Brown et al. 2001). This oxidative stress then appears to stimulate the activation of intracellular signaling pathways, for example those including calcium (Stone et al. 2000), resulting in the increased expression of pro-inflammatory cytokines (Brown et al. in press).

Epidemiological studies also support a role for ultrafine particles in the mechanism by which elevated PM_{10} exposure results in adverse health effects. Peters et al. (1997) counted the number of ultrafine particles in the air in Erfurt, Eastern Germany and found that 73% of the particles were in the ultrafine size range, but that 82% of the mass was attributable to larger particles in the range of 0.1 to 0.5 μm diameter. In adults with a history of asthma, both size fractions were associated with a decrease in peak expiratory flow (PEF), but the effect of the number of ultrafine particles was much stronger (Peters et al. 1997).

Particle size and surface area

More recently, Duffin et al. (2002) measured the ability of several different types of low-toxicity particle to cause a short-term inflammatory response following instillation into the rat lung. Although quite different masses of particle were instilled, there was no relation between the mass of particle instilled and neutrophil recruitment to the lung. Nevertheless, there was a straight-line relation between the surface area dose of particles instilled and the inflammatory response. In contrast, particles with relatively toxic surfaces such as quartz or nickel, did not lie on the straight line linking surface area to number of neutrophils in bronchoalveolar lavage. Instead, these particles induced a greater inflammation than the low toxicity dusts at equivalent surface area doses. This suggests that the inflammogenic potential of these toxic particles was a function of both their surface area and their greater surface reactivity. These findings might imply that the toxicity of PM_{10} could be related to the size distribution of the particles and hence their surface area, as well as the reactivity of the component particles. As yet there is no evidence available to allow toxicologists to untangle the relative role of surface area and surface reactivity in the toxicity of PM_{10} samples because PM_{10} is such a complex mixture containing soluble particles whose contribution to any surface area effect would be short-lived if present at all.

PM_{10} composition and biological reactivity

Preliminary studies carried out in our own laboratory by Lightbody et al. (in press) have compared the inflammogenic potential of PM_{10} samples collected onto Teflon filters using a gravimetric sampler over 24 hours at six locations of the United Kingdom (U.K.) Automatic monitoring network (http:/www.airquality.co.uk). These six sites differ in the predominant source of particulate pollution as described in Table 2. The sites have been characterised by the U.K. Government's Department for Environment, Food and Rural Affairs (DEFRA) using a combination of modelling and screening studies. The mass of PM_{10} collected during 24 hours at each site, was instilled into rats and a bronchoalveolar lavage (BAL) carried out 18 hours later. The PM_{10} samples studied from each site were collected on the same dates. Again the number of neutrophils in the BAL fluid was used as an indicator of inflammation. The relation between the mass of PM_{10} collected over 24 hours and the percentage of neutrophils in BAL fluid was weak (Fig. 1). These findings suggest that variation in composition may explain variations in inflammogenicity of the PM_{10} samples. For example, the inflammation induced by PM_{10} collected at a roadside collection site (Marylebone Road) was frequently high regardless of the 24-hour PM_{10} mass collected. In contrast, the inflammation induced by PM_{10} collected at an industrial location (Port Talbot) was consistently low. Further analysis of the composition of these PM_{10} samples may shed light on which factors make PM_{10} samples of comparable mass dose different in their inflammogenic potential.

A small number of epidemiological studies have also investigated the impact of particulate pollution sources on the health effects of PM_{10}. For example, van Vleit et al. (1997) demonstrated

Table 2 U.K. automatic monitoring network sites used to collect PM_{10} for analysis of biological toxicity. Values in column 3 represent the number of days on which the mean PM_{10} concentration exceeded 50 μg/m³ in the year 2000. The values in column 4 indicate the mean concentration of PM_{10} over the entire year 2000 at each sampling site.

PM_{10} collection site	Site characteristics	Number of 24h mean PM_{10} >50 μg/m³ (2000)	Annual mean PM_{10} μg/m³ (2000)
Belfast	Urban center with considerable fossil fuel combustion sources	8	25
Birmingham	Urban center	4	21
Harwell	Rural	Not available	Not available
Marylebone Road	Roadside London city center street canyon with >80,000 vehicles/day	48	159
North Kensington	Urban background	11	26
Port Talbot	Urban background with considerable industrial sources	61	33

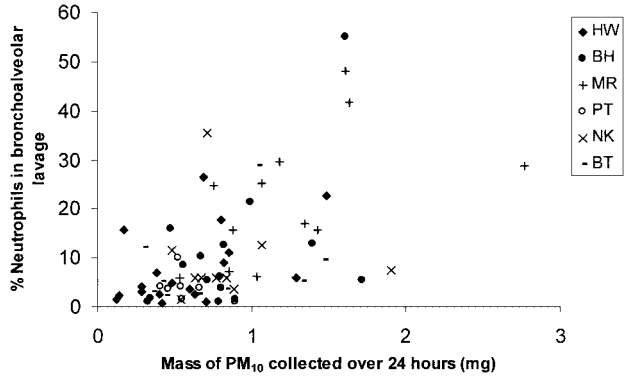

Fig. 1 Percentage neutrophils in the bronchoalveolar lavage cell population expressed as a function of PM_{10} gravimetric mass collected onto each filter. Bronchoalveolar lavage was collected from rats 18 hours after instillation of PM_{10} recovered from a 24-hour filter sample. HW Harwell; BH Birmingham; MR Marylebone Road; PT Port Talbot; NK North Kensington; BT Belfast.

that children attending school less than 1,000 m from major freeways in South Holland reported a higher incidence of cough, wheeze, runny nose and doctor-diagnosed asthma. In a separate study based in England and Wales, Aylin et al. (2001) could not find any significant evidence to link adverse health effects with living in the near vicinity of an operational coke works.

Probably, one of the most widely reported of the epidemiology studies investigating the importance of PM_{10} source, relates to Utah Valley where PM_{10} is dominated by particles derived from the local steel industry. Pope et al. (1992) reported that during closure of the steel mill due to industrial action, there was a drop in the ambient level of PM_{10} and its metal content and also a decrease in the severity of a number of health indicators in the local population. On reopening of the steel mill, the PM_{10} levels increased again, as did their metal content and the associated health effects. Subsequent analysis of the PM_{10} samples before, during and after closure revealed that the closure was indeed associated with a decrease in the transition metal content of the PM_{10}.

Transition metals and PM_{10}

The results of the Utah Valley study lead to the proposal that the metal content of PM_{10} was primarily responsible for its adverse health effects. This hypothesis was supported by toxicological studies using PM_{10} collected before, during and after the steel mill was closed. In early studies aqueous extracts of PM_{10} filters showed that the ability to produce free radicals was greater when the steel mill was open (Frampton et al. 1999). When PM_{10} was added to human epithelial cell lines, samples collected during the open periods of the steel mill stimulated greater production of the pro-inflammatory cytokines interleukin-6 (IL-6) and interleukin-8 (IL-8) and this was related to the metal content of the sample. When the PM_{10} samples were instilled into the lungs of human volunteers (Ghio et al. 2001), those collected when the steel mill was open possessed a greater ability to produce inflammation compared with samples collected when the steel mill was closed.

The toxic effects of metals on the lung have previously been reported in relation to metal fume and metallic dust exposure as a consequence of industrial activities such as welding. Such exposures lead to a range of diseases including acute pneumonitis, pulmonary oedema, COPD, and a fever-like response comparable with the symptoms of influenza (Nemery, 1990).

Metals may induce inflammation in the lung via oxidative stress, however, this depends upon the chemical form of the metal. Metal salts such as sulfates are readily soluble (Ghio et al. 1999), allowing the metal ions to undergo Haber-Weiss and Fenton reactions leading to the generation of highly toxic hydroxyl radicals (Stohs and Bagchi 1995). In contrast, metals *per se* are insoluble, and unless the surface of the metal particle is highly reactive, e.g. ultrafine nickel (Duffin et al. in press) then such particles may exhibit a relatively low toxicity. The lack of neutrophil influx induced by PM_{10} collected from Port Talbot (Fig. 1) may support this suggestion, since Jones et al. (2001) reported that spherical metallic particles occur in these samples.

A large number of studies into the role of transition metal salts in the biological effects of PM_{10} have been conducted using the surrogate particle residual oil fly ash (ROFA), a by-product of oil combustion. Instillation of ROFA into rats produces an inflammation as indicated by an influx of neutrophils into the lung (Pritchard et al. 1996). This inflammation correlated with the metal content and the ability of the ROFA sample to generate free radicals *in vitro*. ROFA—induced inflammation appears to be mediated via the activation of epithelial cells rather than macrophages (Becker et al. 1996). For example, human epithelial cell lines exposed to ROFA generate increased quantities of the pro-inflammatory cytokines such as IL-6 and IL-8 (Carter et al. 1997) as well as stimulating the activation of the oxidative stress responsive transcription factor nuclear factor kappa B (NFκB) (Quay et al. 1998). All of these responses were inhibited by the metal chelator deferoxamine, further supporting the role of metals in the induction of inflammation by ROFA. The cytotoxic and pro-inflammatory

effects of ROFA in epithelial cells can also be ameliorated with the antioxidants tetramethylthiourea and N-acetylcysteine (Dye et al. 1997).

In addition to altering the production of cytokines by epithelial cells, ROFA also enhances MUC2 mRNA expression after 4-hours of exposure, and mucin secretion after 8 hours in guinea-pig tracheal epithelial cells (Jiang et al. 2000). In this study, only vanadium, of all of the soluble transition metals in ROFA including nickel and iron, provoked mucin secretion when added as a pure metal salt. A novel pathway for the pro-inflammatory effects of transition metals was suggested by Samet et al. (1997), who demonstrated that ROFA exposure of pulmonary epithelial cells induces vanadium ion-mediated inhibition of tyrosine phosphatase activity, leading to accumulation of protein phosphotyrosines. This disruption of protein tyrosine phosphate homeostasis could lead to increased synthesis of proinflammatory proteins by airway epithelial cells.

The main disadvantage with using ROFA as a surrogate for PM_{10} is that in terms of composition it is metal dominated and hence the biological effects are therefore likely to be metal mediated. In addition, ROFA is more than 90% soluble (Gavett et al. 1999), which means that its durability in the lung will be considerably different to the majority of particles found in most PM_{10} samples.

Convincing evidence supporting a role for transition metals in the toxicological effects of PM_{10} comes from experiments which have utilized metal chelators and antioxidants to block the effects of metals, as well as from studies where transition metal solutions mimicking the levels found in samples of particles have replicated the levels of inflammation produced by the particles themselves. For example, the metal chelator, deferoxamine, has been used to block free radical production by Edinburgh PM_{10} (Donaldson et al. 1997), and to prevent PM_{10} (Jimenez et al. 2000) and ROFA (Quay et al. 1988) induced NFκB activation and cytokine expression in epithelial cells. In the case of ROFA, vanadium appears to be a key metal in the induction of pro-inflammatory effects on epithelial cells *in vitro* (Carter et al. 1997). However, the importance of vanadium in ambient PM_{10} is yet to be demonstrated.

Particulates can also cause oxidative stress and pro-inflammatory effects, such as TNFα production by macrophages, and these effects are inhibited by transition metal chelators and antioxidants (Goldsmith et al. 1998). In studies by Monn et al. (1999), metal chelators were also reported to protect macrophages from the cytotoxic effects of particles.

Interactions between particles and metals

From the preceding review, it is evident that both ultrafine particles and transition metals could be important mediators of the adverse heath effects of PM_{10} and that they both act via their ability to cause oxidative stress. Therefore it is possible that there are synergistic interactions between transition metals and ultrafine particles (and possibly other components of PM_{10}) leading to inflammation. This would have widespread consequences for understanding the different pathways by which PM_{10} has its adverse effects, as well as for the measurement metric of PM_{10}.

In a study by Wilson et al. (2002) we aimed to investigate potential interactions between transition metal salts and either fine or ultrafine carbon black (CB and ufCB, respectively). In the rat lung, ufCB induced a significant neutrophil influx and this

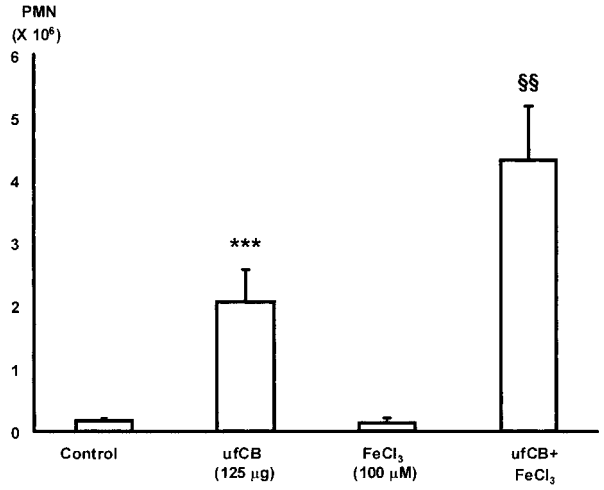

Fig. 2 The number of neutrophils collected per animal by bronchoalveolar lavage,18 hours after an intratracheal instillation of either 125 μg of ultrafine carbon black (ufCB) and/or 0.5 ml of 100 μM ferric chloride ($FeCl_3$). Results represent the mean neutrophil number from three rats. *** $p<0.01$ comparing the number of neutrophils in the bronchoalveolar lavage fluid of control animals (saline only) versus those animals exposed to ufCB. §§ $p<0.05$ for synergistic interaction comparing those animals exposed to ufCB only with those exposed to ufCB and $FeCl_3$.

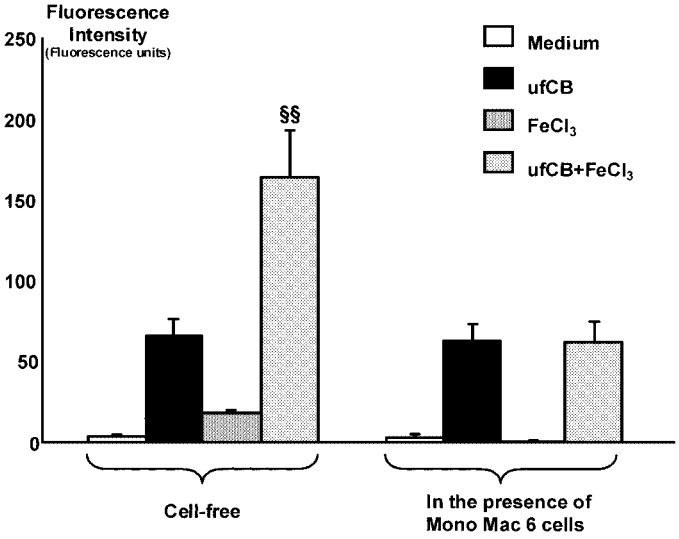

Fig. 3 The effect of adding ferric chloride (final concentration 100 μM) to ultrafine carbon black (ufCB) (final concentration 15 μg/ml) on the oxidation of 2,3-dichlorofluorescin (DCFH) to the fluorescent 2,3-dichlorofluorescein (DCF) in both a cell-free sytsem and in the presence of Mono Mac 6 cells (4×105 cells/ml). Results are expressed as a mean increase in fluorescence over 500 seconds minus corresponding control traces (+SEM) from three experiments. §§ $p<0.05$ for synergistic interaction when comparing the fluorescence intensity induced by ufCB alone with that induced by ufCB with the addition of the metal salts in a cell-free system.

inflammatory effect was synergistically enhanced by co-instillation of $FeCl_3$ (100 μM) (Fig. 2). Due to the suggestion that both ultrafine particles and transition metals induce their proinflammatory effects in the lung through the induction of oxidative stress, the ability of these treatments to generate reactive oxygen species (ROS) was assessed using the fluorescent probe dichlorofluorescin (DCFH). In both the absence and presence of macrophage cells, the ufCB particles were found to possess a greater ability to generate ROS than the same mass dose of CB particles. Addition of

either cupric sulfate ($CuSO_4$), ferrous sulfate ($FeSO_4$) or ferric chloride ($FeCl_3$), synergistically enhanced ROS generation by ufCB, but not CB (Wilson et al. 2002). However, this was only true in the cell-free system (Fig. 3). In the presence of a human monocytic cell line (Mono Mac 6), the ability of both ufCB and CB to generate ROS was not enhanced by the inclusion of soluble iron salts. In addition, ufCB, but not CB was observed to induce a dose-dependent increase in TNFα production by the J774 mouse macrophage cell line. Again this effect of ufCB on macrophages was not further enhanced by the addition of iron salts. The inability of metals to enhance ROS and TNFα generation in the presence of macrophages may be explained by the ability of these cells to chelate iron, a function which is vital in their capacity to degrade aged red blood cells (Emerit et al. 2001).

Endotoxin

Endotoxin instillation into human lungs results in a focal inflammatory response characterised by an early influx of neutrophils with elevated cytokines such as TNFα and IL-6, followed by increased macrophages and monocytes as well as neutrophils. This later phase is accompanied by a fall to basal levels of most mediators (O'Grady et al. 2001).

Endotoxin has been identified as the biologically active component of many dusts such as cotton dust (Keman et al. 1998), grain dust and wool dust (Brown et al. 1996), causing symptoms of bronchitis in many occupational settings.

A number of studies have suggested that the health effects of PM_{10} may be attributed to the bacterial endotoxin content. Soukup and Becker (2001) treated human alveolar macrophages with the soluble and insoluble components of Chapel Hill PM_{10}. The insoluble components of PM_{10} were found to be greater than 50-times more potent than the soluble PM_{10} components at inducing the expression of IL-6 and TNFα. Addition of polymixin B resulted in a small but significant decrease in the effect of the insoluble components of PM_{10} on IL-6 expression. These findings suggest that endotoxin may play a role in the activation of macrophages by Chapel Hill PM_{10}, but that it is not a major factor. In a previous study, Monn and Becker (1999) reported that lipopolysaccharide binding protein completely inhibited cytokine production by $PM_{10\text{-}2.5}$. Further investigations are required to test the disparity between these findings.

Interactions between particles and endotoxin

Few studies have investigated an interaction between the endotoxin and particulate components of PM_{10}. One study was conducted which investigated the effects of carbon black particles in the lungs of aged rats which had been pretreated with endotoxin. The results, however, were not readily interpretable and no firm conclusions can as yet be drawn from this study (Elder et al. 2000).

Organic components of PM_{10}

Volatile organic compounds (VOCs) are present to a variable extent in PM_{10} samples and have been reported to be capable of contributing to oxidative stress (Li et al. 2000, Bonyallot et al. 2001). Even though VOC's are commonly found in PM_{10} (Harrison and Yin 2000) the regulation of pro-inflammatory genes by polycyclic organic hydrocarbons and other organic substances found in PM_{10} has received little attention. However, in one study, cultured RAW 264.7 macrophages exposed to benzo[a]pyrene adsorbed onto carbon black particles exhibited a time-dependent expression and release of TNFα (Chin et al. 1998); importantly neither untreated carbon black nor benzo[a]pyrene alone induced the release of this cytokine protein. This clearly demonstrates an interaction between particles and benzo[a]pyrene that deserves further research.

Interactions between particles and allergens

Due to the widespread problem of asthma and allergens, such as house dust mite antigens in indoor air and pollen in outdoor air, there is potential for interactions between allergens and particles (Donaldson et al. 2000). Indoor air is not well characterised for particles, largely because of the individual variability of indoor environments and the dominant effect of certain sources such as cooking or smoking, and therefore this will be a difficult problem to address. Nevertheless, there have been attempts to demonstrate the 'adjuvant-like' effects of particles. Several studies have indicated that exposure of rats to diesel exhaust particulates results in enhanced eosinophil recruitment, to experimental allergens such as ovalbumin (Takano et al. 1998). Similar experiments have also been conducted using intranasal exposures of mice to carbon black particles (van Zijverden et al. 2001) and ovalbumin. Again, the particles when added in combination with or prior to ovalbumin treatment, enhanced the immune response to ovalbumin. Hence there is limited evidence to suggest that an interaction between particles and allergens warrants further investigation.

Molecular basis of interactions

Interactions between the components described above could occur at several points in the pro-inflammatory cascade. The regulation of cytokines and thereby inflammatory response involves the reduction-oxidation (redox)-sensitive NF-κB (Sen and Packer 1996, Blackwell and Christman 1997). The activation of NF-κB is mediated through kinase cascades that regulate the phosphorylation and subsequent degradation of inhibitory-kappa B (IκBα), the major cytosolic inhibitor of NF-κB. The activation of NF-κB is tightly regulated by redox equilibrium and is recognized to be a key decision point in the initiation of inflammation by particles (Schins and Donaldson 2001). Glutathione (GSH) is the major thiol antioxidant of small molecular weight involved in redox balance and activation of NF-κB (Pineda Molina et al. 2001). The likely effect of the various components of PM_{10} in leading to oxidative stress and NF-κB activation are considered in Fig. 4. Ultrafine particles (Stone et al. 1998) and transition metals (Emerit et al. 2001) cause oxidative stress, which is capable of activating NF-κB in addition to a number of kinases which are oxidative stress-responsive (Sen and Packer 1996). Ultrafine particles have been reported to induce increases in intracellular Ca^{2+} which is also an important signaling event that could synergise with other signaling pathways (Stone et al. 2000). In addition, endotoxin causes oxidative stress and kinase activation (Victor et al. 2002). We also recently reported that PM_{10} might act on more than one target cell to amplify the inflammatory response (Jimenez et al. 2002). In this study, we demonstrated that macrophages treated with PM_{10} released IL-1 and TNFα. The medium collected from these macrophages was used to treat epithelial cells resulting in

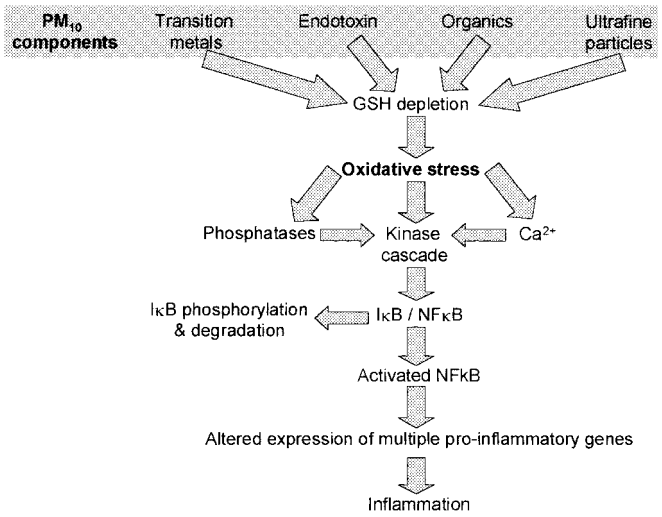

Fig. 4 Schematic diagram of the components of PM_{10} and their biological targets. Interactions may occur at the level of oxidative stress, at the molecular signaling level, and/or between inflammatory mediators.

activation of both NF-κB and IL-8 due to the stimulatory activities of IL-1 and TNFα. Hence the potential for multiple interactions between the components of PM_{10}, different lung cells and pro-inflammatory mediators is complex. It is possible that endotoxin might, for example, activate secretion of pro-inflammatory cytokines by macrophages which then stimulate epithelial cells, while transition metals might act primarily on epithelial cells, which when activated by the macrophage cytokines, release increased amounts of chemokine (Wilson et al. 2002). The limited evidence available so far suggests that these interactions result in a synergistic response, which requires further investigation. The potential for antagonistic or simple additive interactions between the components of PM_{10} may also be viable.

Summary/conclusion

In conclusion, the biological effects of PM_{10} can be attributed to a number of candidate components. Common mechanisms and pathways have been identified that raise the distinct possibility that interactions between these components could occur in biological systems. However the relative importance of these interactions, which could drive the molecular events leading to heightened inflammation, remain to be elucidated. A better understanding of these factors may in future be used to regulate the emission of components of PM_{10} rather than the overall mass.

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