

Review

Diesel exhaust as a model xenobiotic in allergic inflammation

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Abstract

We investigated the effects of diesel exhaust particulates on the human allergic response using in vivo human nasal challenges. Diesel particles and phenanthrene, one of their constituent polyaromatic hydrocarbons, were shown to enhance total allergic antibody (IgE) production, enhance allergen-specific IgE in the presence of allergen, and induce sensitization to a neoantigen. © 2000 Elsevier Science B.V. All rights reserved.

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1. Particulates from fossil fuel combustion are common and linked to allergic airway disease

Large surveys have documented the increase in upper airway allergic disease during the end of the 20th century with prevalence rates going from less than 5% to 20% in the 1980s (Fleming and Crombie, 1987). We sought to investigate the role of diesel exhaust particles (DEP) as a model xenobiotic air pollutant in these changes. The increase in nasal allergies has been a global phenomenon observed in industrializing countries (Aberg, 1989). Changes in the air quality related to airborne “pollutants” are likely one critical factor in the increasing worldwide incidence, prevalence, and severity of allergic airway disease. DEP can serve as a model for airborne

particulates containing xenobiotics such as polyaromatic hydrocarbons (PAH) and monofunctional inducers of oxidative stress (MIOS) (Nel et al., 1998; Ng et al., 1998). DEP make up, on average, 40% of the 10- μ m particles (PM10) in a city such as Los Angeles. DEP are representative of PAH/MIOS containing particulates generated from a variety of human activities, e.g. burning of fossil fuels and cigarette smoking. They are comprised of an inert carbon core containing unburnt fuel petrochemicals (Barfknecht et al., 1982).

2. Human allergic inflammation in response to DEP and PAH/MIOS

We have employed a human in vivo nasal challenge model to investigate the effects of DEP and the chemical contained therein upon allergic inflammation. Results from these studies are summarized in the following table.

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Effects of DEP on human in vivo allergic responses

Diesel exhaust particles

- Enhance local mucosal IgE production
- Induce an inflammatory response of cells, chemokines and cytokines
- PAH enhance local mucosal IgE production without a measurable cellular inflammatory response

DEP plus allergen

- Enhance local antigen-specific IgE production
- Deviate cytokine production toward a Th2 profile
- Drive in vivo isotype switch to IgE

DEP plus neoantigen

- Synergize to drive primary mucosal sensitization to KLH

3. DEP increase mucosal IgE production (Diaz-Sanchez et al., 1994, 1996, in press)

We initially demonstrated that DEP induced enhanced IgE production in vivo following intranasal challenge with the amount of DEP (100 mg) inspired in 1–3 days in Los Angeles. DEP was shown to drive mucosal chemokines production from non-T cells within hours of in vivo DEP exposure. Maximal DEP-enhanced expression for RANTES and MCP-3 was at 2 h followed by a peak of MIP-1 α at 4–6 h. All had returned toward baseline by 24 h. In contrast, DEP did not enhance expression of eotaxin at any time demonstrating that the action of DEP was not simply a global effect on all CC chemokines. Challenge with DEP also resulted in an increase in total and mononuclear cell counts in nasal lavage fluids and a significant enhancement of eosinophil cytotoxic protein levels at 6–24 h after challenge. Following DEP nasal challenge, there was a markedly increased naïve T cell (TH0-like) cytokine production at 24 h.

4. DEP plus allergens increases mucosal antigen-specific IgE production (Diaz-Sanchez et al., 1997)

Challenge with a combination of allergen (Ragweed) plus DEP was employed to mimic the effects of DEP on an established allergen-specific

IgE response. Initially, short ragweed, an antigen not present in California, was given in increasing doses intranasally to subjects who had a demonstrated positive short ragweed skin test. Doses were established that led to a positive nasal challenge. This was associated with a small increase in IgE and anti-ragweed IgE in the nose but did not induce a change in local cytokine production. Co-administration of DEP plus ragweed led to a surprising TH2-like deviated cytokine production with a fall in gamma interferon production compared to DEP alone, along with a dramatic boost (50-fold) in allergen-specific IgE production. DEP alone did not increase ragweed-specific IgE. Following the combined challenge, we observed the early appearance (4 h) of IL-4 protein following these challenges, an effect that could be responsible for deviating the response toward a TH2-like pattern. We have shown that this early production of IL-4 is from c-kit (CD117) positive cells that are probably local basophils–mast cells. At the same time, we observed the appearance of other laboratory markers of basophil–mast cell degranulation as well as an enhanced clinical response to allergen in the presence of DEP. Thus, DEP appears to be able to interact either directly or indirectly with basophils–mast cells to lead to their activation and thereby modify the subsequent response to coexposure to allergen.

5. DEP plus allergen induces IgE switch recombination in the secondary humoral immune response (Fujieda et al., 1998)

We have also provided evidence that local DEP exposure drives in vivo isotype switching to IgE following nasal challenges. Detection of deleted switch circular DNA (switch circles) was employed as definitive molecular evidence of Ig isotype switching. Four days after combined intranasal DEP plus ragweed challenge, we detected and characterized clones of deleted switch circular DNA (S_{ϵ}/S_{μ}) representing switching from μ to ϵ in mucosal B cells. No switch circular DNA was detected in nasal lavage cells following challenge with DEP alone nor with ragweed allergen alone. These results indicate that the combination of mucosal stimulation with DEP and ragweed allergen is capable of driving in

vivo isotype switching to IgE in humans with ragweed allergy.

6. PAH found in DEP have effects distinct from simple particulate effects.

Nasal provocation challenge of subjects with 0.3 mg carbon black resulted in influx of inflammatory cells into the nasal mucosa. An increase in the number of neutrophils, mast cells and especially lymphocytes and monocytic cells was apparent from 6 to 24 h following challenge. However, in contrast to DEP, there was no increase in IgE levels in nasal lavage fluid present at 24 h and 4 days after the carbon black challenge. Conversely, when subjects were challenged with 60 µg of phenanthrene, a dose comparable to the amount of phenanthrenes present in our standard DEP challenge, no cellular influx was observed at any time out to 7 days. On the other hand, phenanthrene alone did induce a significant rise in total IgE production detectable at 4 days as was seen with DEP. In ragweed-sensitive subjects challenged with both phenanthrene plus ragweed, the levels of local ragweed-specific IgE were also significantly elevated as compared to the response seen in such individuals challenged with ragweed alone. The overall increase in total IgE and ragweed-specific IgE in the phenanthrene challenge experiments was approximately 50% of that observed with DEP.

7. DEP exposure with a neoantigen leads to sensitization IgE mucosal IgE production

To determine if DEP could synergize with a neoallergen to drive the de novo production of antigen-specific IgE (e.g. sensitization), a series of in vivo nasal challenges were undertaken. Initially, a protocol was developed employing intranasal inoculation with keyhole limpet hemocyanin (KLH). Subjects challenged with 1 mg of KLH followed by 100 µg weekly for a total of 3 weeks were shown to develop an IgG and IgA anti-KLH response detectable in the nasal lavage fluid. In contrast, subjects who received the identical KLH challenges in the presence of DEP mounted a vigorous IgE anti-KLH response by week 4. Surprisingly, DEP plus

KLH exposure did not lead to an increase in the local production on IgA or IgG anti-KLH although the levels of IgG4 to KLH did increase. Thus, DEP co-administration was capable of driving an IgE response to this neoantigen, whereas exposure to the potential allergen alone did not.

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References

- Aberg, N., 1989. Asthma and allergic rhinitis in Swedish conscripts. *Clin. Exp. Allergy* 19, 59–63.
- Barfknecht, T.R., Hites, R.A., Cavaliers, E.L., Thilly, W.G., 1982. Human cell mutagenicity of polycyclic aromatic hydrocarbon components of diesel emissions. *Dev. Toxicol. Environ. Sci.* 10, 277–294.
- Diaz-Sanchez, D., Dotson, A.R., Takenaka, H., Saxon, A., 1994. Diesel exhaust particles induce local IgE production and alter the pattern of IgE messenger RNA isoforms. *J. Clin. Invest.* 94, 1417.
- Diaz-Sanchez, D., Tsien, A., Casillas, A., Dotson, A.R., Saxon, A., 1996. Enhanced nasal cytokine production in human beings after in vivo challenge with diesel exhaust particles. *J. Allergy Clin. Immunol.* 98, 114–123.
- Diaz-Sanchez, D., Tsien, A., Fleming, J., Saxon, A., 1997. Combined diesel exhaust particulate and ragweed allergen challenge markedly enhances in vivo nasal ragweed-specific IgE and shows cytokine production to a TH2-type pattern. *J. Immunol.* 158, 2406–2413.
- Diaz-Sanchez, D., Jyräla, M., Ng, D., Nel, A., Saxon, A., in press. In vivo nasal challenge with diesel exhaust particles enhances production of the CC chemokines RANTES, MIP-1α, and MCP-3 in humans. *Am. J. Respir. Mol. Biol.*
- Fleming, D.M., Crombie, D.L., 1987. Prevalence of asthma and hay fever in England and Wales. *Br. Med. J.* 294, 279–283.
- Fujieda, S., Diaz-Sanchez, D., Saxon, A., 1998. Combined nasal challenge with diesel exhaust particles and allergen induces in vivo IgE isotype switching. *Am. J. Respir. Mol. Biol.* 19, 507–512.
- Nel, A.E., Diaz-Sanchez, D., Ng, D., Hiura, T., Saxon, A., 1998. Enhancement of allergic inflammation by the interaction between diesel exhaust particles and the immune system. *JACI* 102, 539–554.
- Ng, D., Kokot, N., Hiura, T., Faris, M., Saxon, A., Nel, A., 1998. Macrophage activation by polycyclic aromatic hydrocarbons: evidence for the involvement of stress-activated protein kinases AP-1 and anti-oxidant response element. *J. Immunol.* 161, 942–951.