Extramural Research

2005 Progress Report: Pollution-Enhanced Allergic Inflammation and Phase II Enzymes

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EPA Grant Number: R831861C002
Subproject: *this is subproject number 002 , established and managed by the Center Director under grant R831861*
(EPA does not fund or establish subprojects; EPA awards and manages the overall grant for this center).
Center: USC Center for Children's Environmental Health
Center Director: Gilliland, Frank
Title: Pollution-Enhanced Allergic Inflammation and Phase II Enzymes
Investigators: Gilliland, Frank
Current Investigators: Gilliland, Frank , Diaz-Sanchez, David
Institution: University of Southern California
EPA Project Officer: Callan, Richard
Project Period: November 1, 2003 through October 31, 2008 (Extended to October 31, 2010)
Project Period Covered by this Report: November 1, 2004 through October 31, 2005
RFA: Centers for Children's Environmental Health and Disease Prevention Research (2003)
Research Category: Children's Health , Health Effects

Description:

Objective:

The objective of this research project is to study the role of Phase II enzymes in regulating responses to pollutants in: children's upper airways (Aim #1); the lower airways of healthy and asthmatic individuals (Aim #2); and mechanistic animal and cellular models of allergic inflammation (Aim #3).

Progress Summary:

Aim #1

We plan to determine whether nasal challenge with diesel exhaust particles (DEP) will induce reproducible gene expression of Phase II enzymes and compare expression in children versus adults. Previously, we had shown that challenge of individuals with DEP-induced *GSTM1* expression in adults. In preparation for the main part of this aim, we have developed real-time quantitative polymerase chain reaction to measure gene expression of the other sentinel Phase II enzymes that we will use in the study, *NQO1*, and validated its use. We identified eight adult individuals who had functional versions of *NQO1* polymorphisms and challenged them with either DEP (300 µg) or saline during separate visits spaced 3 weeks apart. Three weeks later, the subjects were recalled and challenged with DEP again. Cells were obtained from nasal lavages performed before or 24 hours following each challenge.

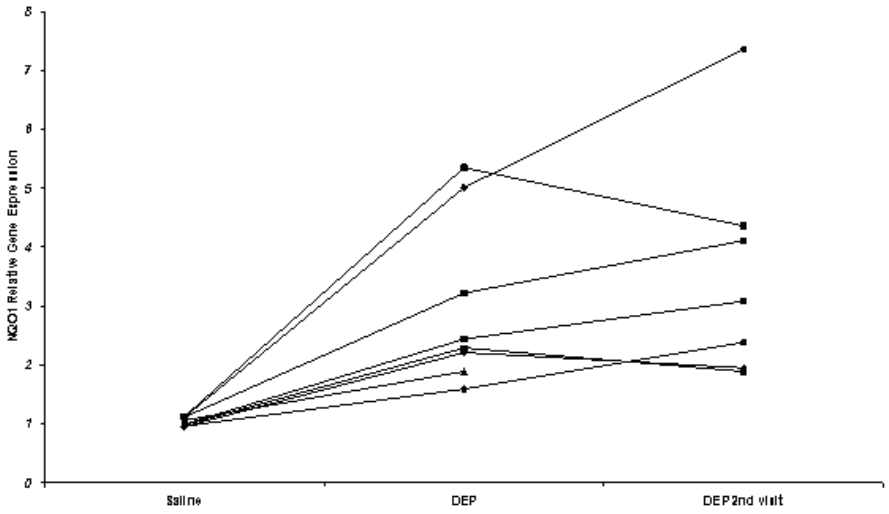

Figure 1. Relative Levels of *NQO1* Gene Expression After Normalization to an Internal Control

Figure 1 shows the relative levels of *NQO1* gene expression after normalization to an internal control from eight subjects. In each case, control expression (i.e., that seen in cells from lavages after challenge with saline) of the genes was given an arbitrary figure of 1.0, and the relative expression was calculated with reference to baseline. In all cases, *NQO1* increased, as was the case for *GSTM1* gene expression; although there was considerable interindividual expression of *NQO1*, intraindividual expression was considerably less.

Aim #2

As proposed in our timeline, we intend to commence studies on the effect of Phase II on the lower airway response to diesel in Year 2 of the project. We have tested the exposure chamber and can reproducibly produce a DEP level that is within 10 percent of the target level every time. We can measure accurately particle mass, number, size, and composition generated by the diesel engine.

Aim #3

We had shown previously that enhancement of Phase II enzyme expression could inhibit enhancement of IgE production by peripheral blood cells *in vitro*. In those experiments we used sulforaphane, a potent inducer of Phase II enzymes found in cruciferous vegetables, which functions by activating Nrf2. We tested whether this same reagent could block DEP-mediated adjuvant events *in vivo*. Groups of six female BALB/c mice matched for age and weight (10-12 weeks) received aerosolized exposures to either: saline, ovalbumin (OVA) (1% 20 minutes), DEP (1 hour), or OVA followed immediately by DEP for 10 consecutive days. Mice were administered either vehicle (corn oil) or sulforaphane (4.5 µmol/mouse/day) by gavage (0.2 ml) for 1 week prior to the commencement of exposures up until 2 days after the last exposure.

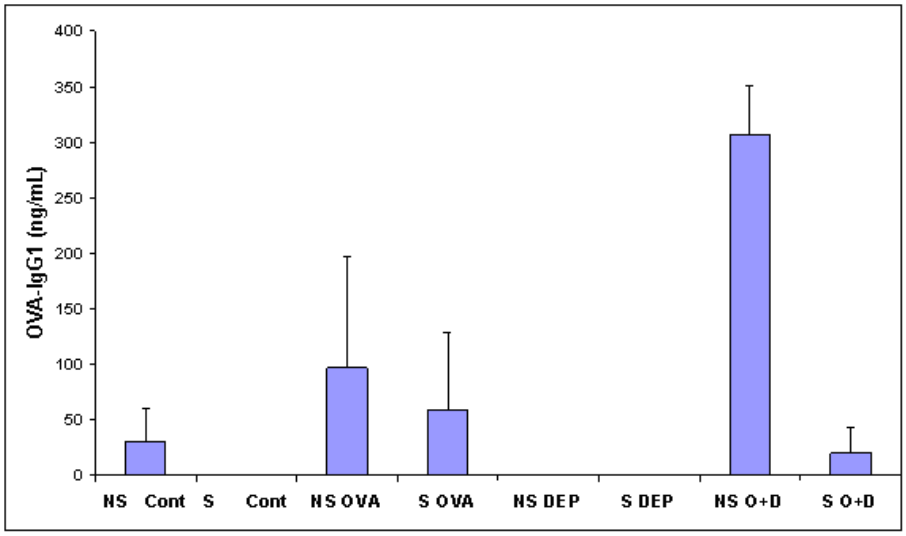

Figure 2. Serum Levels of IgG1 14 Days After Allergen Exposure in Mice Given Sulphoraphane (S) or No Sulforaphane (NS)

Figure 2 shows serum levels of the antigen-specific allergic antibody IgG1 14 days after allergen exposure in mice given sulforaphane or no sulforaphane. As expected, in the untreated group, IgG1 levels were significantly higher in mice that received both DEP and OVA than in those that were exposed to OVA alone. Administration of sulforaphane, however, completely ablated the adjuvant effects of DEP.

Significance

Our results show that Phase II enzymes can be induced by our model air pollutant, DEP, and are critical in regulating responses and determining susceptibility to these xenobiotics. These promising results also suggest a possible intervention strategy to augment the body's natural defense to air pollutants.

Future Activities:

During Year 3, we intend to recruit adults and children for Aim #1, commence recruitment for Aim #2, and repeat our mouse/sulforaphane experiment in Nrf-2 knock-out mice to confirm that the action of sulforaphane is indeed through activation of Nrf-2.

Journal Articles:
No journal articles submitted with this report: View all 5 publications for this subproject

Supplemental Keywords:

asthma, children, susceptibility, community, children's health, health effects, risk assessment, airway disease, allergen, asthma, childhood respiratory disease, children's environmental health, community-based intervention, outreach and education, respiratory problems,, HUMAN HEALTH, ENVIRONMENTAL MANAGEMENT, Scientific Discipline, RFA, Health, Health Effects, Risk Assessment, Health Risk Assessment, Children's Health, Biochemistry, allergen, respiratory problems, children's environmental health, childhood respiratory disease, susceptibility, outreach and education, community-based intervention, airway disease, asthma, Human Health Risk Assessment

Relevant Websites:

http://www.usc.edu/schools/medicine/research/centers_programs/cehc/ EXIT Disclaimer

http://www.usc.edu/schools/medicine/departments/preventive_medicine/divisions/occupational/occ_environmental/cehc/index.html EXIT Disclaimer

Progress and Final Reports:

Original Abstract
2004 Progress Report
2006 Progress Report

Main Center Abstract and Reports:

R831861 USC Center for Children's Environmental Health

Subprojects under this Center: (EPA does not fund or establish subprojects; EPA awards and manages the overall grant for this center).

R831861C001 Urban Air Pollution and Persistent Early Life Asthma
R831861C002 Pollution-Enhanced Allergic Inflammation and Phase II Enzymes
R831861C003 Air Pollution, Exhaled Breath Markers, and Asthma in Susceptible Children