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Children's Environmental Health Center

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INVESTIGATORS: Frank Gilliland, Rob McConnell, David Diaz-Sanchez, Marc Riedl, Edward Avol, W. James Gauderman, Andrea Hricko, John Peters, William Linn, Fred Lurmann

INSTITUTIONS: University of Southern California (USC) and University of California, Los Angeles (UCLA)

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DESCRIPTION

The Children's Environmental Health Center (CEHC) was established in 1998 to investigate effects of the environment on children's respiratory health, with a focus on asthma and airway disease. The theme of the Center and its research focus were chosen based on the clinical and public health importance of childhood respiratory diseases and the potential importance of common environmental exposures on the etiology of these conditions, especially among susceptible subgroups of children. The Center also established a community outreach and translation program to translate research findings to communities and inform policymakers about the effects of the environment on children's health.

OBJECTIVES OF RESEARCH

The broad objectives of the Center's research activities during its second cycle were:

1. To investigate the role of regional ambient air pollutants such as O_3 and locally emitted fresh vehicle exhaust in airway inflammation and in asthma occurrence during childhood;
2. To investigate the mechanism for the modulating effects of ambient air pollutants on allergic inflammation in children;
3. To assess genetic variation as a determinant of childhood respiratory susceptibility to regional ambient air pollutants such as O_3 or locally emitted fresh vehicle exhaust;
4. To understand the local and regional variation in ambient air pollution and how it impact the burden of airway disease in children;
5. To implement a community-based participatory research program to respond to community concerns about the effects of ambient air pollutants such as O_3 and locally emitted fresh vehicle exhaust on early life asthma; and
6. To translate the Center's research findings into public health action and policy through a burden of disease assessment and provide a scientific resource for the broader community involved in protecting children's environmental health through community translation and outreach and a CBPR project.

SUMMARY OF FINDINGS

Over the years since the CEHC's founding, we have made major contributions in multiple timely and important scientific and translational arenas, including four areas highlighted in the following sections:

(1) Identifying clinically significant adverse effects of ambient air pollution on children's respiratory health;
(2) Demonstrating that common genetic variants are major contributors to children's susceptibility to environmental stressors;
(3) Defining important pathophysiologic mechanisms for the chronic effects of air pollutants on children's respiratory health; and
(4) Translating research findings to elevate environmental health effects into an essential element for decision-making in urban planning and economic development in Southern California.

Identifying Clinically Significant Adverse Effects of Ambient Air Pollution on Children's Respiratory Health

As described in several high-impact publications, we have observed that children exposed to elevated levels of ambient air pollutants including ozone, PM, NO_2 and fresh traffic-related emissions show clinically important adverse effects on asthma pathogenesis, lung function development, respiratory symptoms and infections.[1-13] The Center facilitated the multidisciplinary collaborations that led to the development of cutting-edge exposure assessment methodology integrating spatial statistics, home-based measurement of air pollutants, environmental multilevel statistical modeling, geographical information systems (GIS), meteorology, and epidemiology. Several important papers documenting the adverse respiratory health effects of regional pollution relied on data developed by the exposure assessment core from measurements at regional monitoring sites and statistical models developed for these analyses.[1, 9-10, 14] In order to assess the impact of local exposures due to fresh traffic emissions, new residential and school exposure indices were developed, based on traffic volume, wind speed and direction and mixing layer height, using a GIS system. Using these models, we have demonstrated associations of asthma prevalence and incidence with traffic-modeled pollution and proximity to major roadways.[3, 6] We have now collected pollution data from a dense network of locations in each of our study communities. Using these measurements and spatial statistical techniques in a Bayesian framework, we have developed new methods for examining effects of traffic-related air pollution.[15] With the development of sophisticated statistical techniques and the advancement of exposure assessment technology (neither of which would have occurred without Center support) we were able to identify independent adverse pulmonary effects from both regional and local pollution.[5] This observation will clearly have an impact on the policy approaches to dealing with this dual problem.

Demonstrating that Common Genetic Variants are Major Contributors to Children's Susceptibility to Environmental Stressors

The task of decreasing children's susceptibility to air pollution offers an important strategy that can be used to target public health prevention efforts. Emerging research indicates that modifiable antioxidant defenses may be an important response to air pollution. Airborne particulate pollutants, such as DEPs, are thought to exacerbate lung and cardiovascular diseases through induction of oxidative stress.[16] The role of genes involved in oxidative stress produced

by xenobiotics (phase II enzymes) has been examined by using GST genotypes, including *GSTM1* and *GSTT1*, which have a null genotype resulting in no protein product, and *GSTP1*, which has a well-studied functional variant (Ile105Val). In individuals with *GSTM1*-null or *GSTP1*-Ile105 genotypes, DEPs enhanced nasal responses to allergen.[17] Compared to subjects with a functional *GSTM1* genotype, *GSTM1*-null subjects had significantly larger increases in IgE levels (146 vs 13.5 U/mL; $P < .01$) and histamine levels (13.9 vs 6.1 nmol/L; $P = .03$) after a DEP plus allergen challenge. The wild-type *GSTP1* genotype was associated with increased IgE levels (149 vs 29.6 U/mL; $P < .01$) and histamine levels (14.5 vs 6.1 nmol/L; $P = .01$) after the same challenge. None of the GSTs modified the response to allergen alone. Common polymorphisms in *GSTM1* and *GSTP1* powerfully modify the adjuvant effect of DEPs on allergic inflammation and identify a large population susceptible to adverse health effects of DEP exposure.

Defining Important Pathophysiologic Mechanisms for the Chronic Effects of Air Pollutants on Children's Respiratory Health

A growing body of evidence indicates that acute and chronic inflammation contributes to the pathogenesis of several common respiratory diseases and conditions.[18-21] Oxidative and nitrosative stress play important roles in regulating immune responses and subsequent tissue responses. Oxidative/nitrosative stress occurs when oxidant and/or nitrosant burden exceeds the buffering capacity of airway antioxidant/nitrosant defenses.[22] In the previous grant period, we investigated whether high ambient air pollutant exposures are associated with airway inflammation as assessed by exhaled nitric oxide (FeNO measured at the conventional 50ml/sec flow rate) in more than 2700 children. We found that exposures to $PM_{2.5}$ mass concentration (seven-day average prior to the test) were associated with increased FeNO. We then investigated whether genetic variants were associated with airway inflammation and children's susceptibility to airway inflammation from ambient air pollution. We found substantial evidence that variation in several genes in the NO synthesis pathway including *NOS2A* and *ARG2* are associated with FeNO, susceptibility to air pollution, risk of new onset asthma and lung function growth. Lastly, we determined that children with chronic airway inflammation as indicated by elevated FeNO are at a greater than two-fold increased risk for new onset asthma. The Center's studies of eNO, along with the studies of genetic variants in oxidative stress and inflammatory pathways provide strong support for the role of oxidative/nitrosative stress in mediating the effects of ambient air pollution.

One approach to reducing the effects of air pollutants such as DEPs is through induction of enzymatic antioxidant defenses, especially in individuals with at-risk genetic variants of key antioxidant enzymes. A prototype for this approach is dietary induction of phase II metabolic enzymes to protect against DEPs. In a proof-of-principle study, dietary sulforaphane, a potent inducer of phase II enzymes, was shown to increase enzyme expression and reduce inflammatory responses.[23] In an in vitro cell system, Wan and Diaz-Sanchez[23] investigated whether sulforaphane stimulated phase II enzyme induction and subsequently reduced the effect of diesel extracts on cytokine production. Sulforaphane increased *GSTM1* and *NQO1* expression, as well as GST activity, while reducing cytokine production. In primary bronchial epithelial cells, sulforaphane also blocked the increased production of interleukin 8, granulocyte-macrophage colony-stimulating factor, and interleukin 1β from primary human bronchial epithelial cells. DEPs have been shown to increase the production of IgE for *in vitro* cell systems and human nasal challenges. The induction of phase II enzymes in B cells by sulforaphane has been shown

to reduce the ability of DEPs to increase IgE production.[23] Dietary sulforaphane also increases phase II enzyme expression in nasal cells. These results suggest that sulforaphane or other compounds that induce phase II enzymes have promise as air pollution chemopreventive agents.[24] These chemopreventive effects also might be available through dietary modification. Further research is needed to determine whether the adverse effects of air pollution can be reduced through interventions tailored to individual genetic susceptibility.

Translating Research Findings to Elevate Environmental Health Effects into an Essential Element for Decision-Making in Urban Planning and Economic Development in Southern California

Decisions about urban planning and regional economic development have important long-term implications for children's health, and in general, have not considered the impacts of exposure to environmental air pollution. Major decisions about the urban infrastructure in Southern California and the changing global economy present an opportunity for the Center to have lasting impacts on children's health by translating Center findings about the adverse effects of air pollution to decision-makers and stakeholders. The Community Outreach and Translation Core (COTC) has succeeded in discussing environmental health as a central consideration in the debate about alternative development scenarios, creating effective programs for translation of the scientific findings, and providing community members and groups with the knowledge and tools needed to allow these stakeholders to more effectively have their concerns heard. This high-impact effort has the potential to improve health and prevent disease in millions of children for generations to come.

At the inception of our Center in 1998, the issue of air pollution from the ports and goods movement was not a high priority for regulatory agencies, scientists or even many community residents in the harbor area. The volume of cargo containers handled at the Ports of Los Angeles and Long Beach has doubled since that time. Today these adjacent ports are the largest port complex in the United States and the number one single source of air pollution in the region, in part due to lack of emission regulations on foreign-flagged ships and the use of older diesel trucks to transport containers out of the Ports. Even with the economic slowdown, the Ports continue to anticipate a doubling of Asian imports into the Ports by the year 2030. Plans are underway to expand marine terminals, freeways, rail yards and other transportation infrastructure to accommodate the flow of goods (half of which are destined for other parts of the country). The COTC and Center investigators first became aware of the emerging situation in 2001 by listening to residents of port communities at our NIEHS Town Meeting, co-sponsored by the CEHC. Since 2001, the COTC has worked to integrate concerns about air pollution's adverse health impacts and related health costs into transportation and land-use decisions, where health concerns previously have seldom been a priority. This effort has led to the participation of center investigators Andrea Hricko and Ed Avol in dozens of regional planning, regulatory, port, and transportation committee meetings. The COTC has also educated dozens of community groups about relevant research findings. Our Center has been recognized for its expertise on the environmental health impacts of international trade, ports and goods movement, by appointment of the COTC director to US EPA's National Environmental Justice Advisory Council's "Goods Movement Work Group," and appointment of Center investigators Hricko and Avol to formal stakeholder committees of the Ports and Metropolitan Transportation Authority.

SUMMARY OF FINDINGS FROM INDIVIDUAL PROJECTS

Project 1: Urban Air Pollution and Persistent Early Life Asthma

Hypotheses

1. Prevalent asthma with early onset (in the first 5 years of life) is strongly associated with early life traffic within 100 m of the child's home.

2. Early onset asthma is independently associated with variation of NO, NO_2 and ozone within communities, which represent regional products of atmospheric photochemical oxidation of traffic related pollutants, but which also vary locally with traffic.

3. The effects of air pollutants on asthma risk in children are modified by polymorphisms in GSTM1, GSTP1, NQO1, HO-1, and TNFα, genes involved in response to oxidant air pollutants.

Specific Aims

To assess Hypotheses 1 & 2:

1. Identify the population for the proposed case-control study
    a. Within the 13 study communities, use existing survey information to identify all kindergarten and first grade children, who have lived in the same residence since before age 2;
    b. Promote participation through the presentation of the Center video, "A Breath of Air," by Community Study Liaisons to school nurses, and to parent organizations and interested teachers.
    c. Identify all children with asthma that have been active during the previous 12 months (N approximately 160) and a sample of children without asthma, matched on age, sex, race/ethnicity and community
2. Collect information from parents of participants to assess asthma, activity patterns, and risk factors for asthma, using a structured telephone interview, also to be administered by Community Study Liaisons;
3. Assess the relationship between traffic within 100 meters of each child's home and asthma among cases and controls, using information from the Exposure Assessment and Modeling Core;
4. Assess the relationship between residential exposure to ambient traffic related air pollutants and asthma among cases and controls, using information from the Exposure Assessment and Modeling Core;
5. Develop tools for assessment of traffic within 100 meters of homes with COTC Neighborhood Assessment Teams composed of community volunteers selected by community research partners;

To assess Hypothesis 3:

6. Genotype cases and controls for polymorphisms in GSTM1, GSTP1, HO-1, NQO1 and TNFα, and assess how these polymorphisms modify the relationship between air pollutants and asthma;

To promote effective communication between partners and to promote broader exchange with the community-based coalitions:

7. Assess the burden of asthma-related disease attributable to air pollution in all children living in two communities represented by the community partners, using results from this study and from existing literature;
8. Develop a series of community forums with the COTC to discuss the public health burden of air pollution for asthma;
9. Integrate new information on air pollution into the environmental action plans developed with families of children with asthma by all community health workers working in service programs of community partners;
10. Foster discussion among partners through an active steering committee and through presentation of results at meetings of partner organizations;
11. Participate with the COTC in seminars, community forums and in the critique of policy initiatives by providing the best scientific evidence available on air pollution and childhood asthma.

Accomplishments

In the last five years, we have evaluated three hypotheses about traffic-related air pollution: (1) Prevalent asthma with early onset (in the first 5 years of life) is strongly associated with early life traffic within 100 m of the child's home; (2) Early onset asthma is independently associated with variation of NO, NO_2 and ozone within communities, which represent regional products of atmospheric photochemical oxidation of traffic related pollutants, but which also vary locally with traffic; (3) The effects of air pollutants on asthma risk in children are modified by polymorphisms in GSTM1, GSTP1, NQO1, HO-1, and TNFα, genes involved in response to oxidant air pollutants.

We found early life asthma that was symptomatic during the year prior to study entry at age 5-7 was associated with traffic proximity and with NO, NO2 and NOx estimated from dispersion models and traffic volume. There was a dose-response relationship between distance to traffic corridors, with increased risk beginning approximately 200 m from a major road and increasing approximately linearly with proximity. The odds ratio was 1.6 for asthma within 75 m of major roads (including freeways, highways and major arterials) where 15% of all participants lived. Risk was larger in children with early life (and longer duration) exposure based on residence at the same address since age 2.

Susceptible groups were identified, including increased risk in girls, consistent with previous literature. Risk of asthma symptoms, severity and prevalence (or asthma incidence in independently funded related work) associated with traffic-related local or regional air pollution was found to be modified by genetic variants involved in oxidative/nitrosative stress pathways, including GSTM1 and P1, TNFα, and EPHX1.

The associations of lifetime asthma with NO_x, NO_2 and ozone measured in a case-control study were not significant. However, based on these and additional measurements at a total of over 1000 locations across Southern California improved models predicting spatial surfaces of these pollutants in our study communities based on traffic distance, volume, meteorology, population density, and other nearby land use. Predicted exposure to NO_x was associated with asthma and

strongly associated with novel wheezy phenotype based on number and severity of symptoms. Regional pollution was not associated with asthma across study communities, after adjusting for local traffic-related exposure, although ozone was found to modify the effect of genetic variants on the risk of asthma and asthmatic bronchitis.

Conclusions

This study was conducted as a community based participatory research (CBPR) project in close coordination with COTC goals to develop community capacity to understand and apply research results to policy related prevention. In this context novel risk assessment methods were developed that identified a several-fold increase in air pollution-related emergency room visits and other severe asthma morbidity likely to result from increased asthma rates due to traffic proximity in the study communities of Long Beach and Riverside. Work with community partners to develop estimates of traffic volume on major traffic corridors has led to novel pilot work by Center investigator Scott Fruin to use these methods to improve our prediction model surfaces.

Project 2: Pollution-Enhanced Allergic Inflammation and Phase II Enzymes

Specific Aims

1. We will test the hypothesis that Phase II enzyme expression in the upper airways are induced by oxidant pollutants and differ between children and adults.
2. We will test the hypothesis that Phase II enzyme expression in the lower airways are induced by oxidant pollutants and differ between asthmatic and non-asthmatic subjects.
3. We will determine the role of Phase II enzymes in regulating the adjuvant effects of PM.

Accomplishments

Aim 1

We had previously shown that challenge of individuals with diesel exhaust particles (DEP) induced GSTM1 expression in adults. We developed real-time quantitative PCR (RT-PCR) to measure gene expression of NQO1, GSTM1, GSTP1 and HO-1 from cells recovered from nasal washes. We recruited a total of 20 adult subjects and performed a double-blind randomized cross-over study to test the expression of these enzymes in response to nasal challenge with four different DEP doses (0, 30, 100, or 300 µg). Subjects performed nasal lavage sampling immediately before and 24 hours after each DEP challenge. DEP was administered by nasal spray into one nare via an atomizer. Each subject was randomized to one of 24 possible sequences of 4 DEP exposures. A four-week wash-out period was observed between each DEP exposure. All subjects had fully functional versions of GSTM1

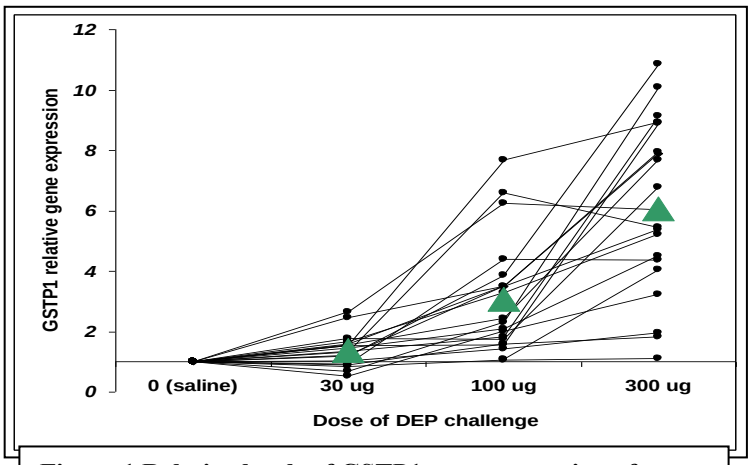

Figure 1 Relative levels of GSTP1 gene expression after normalization to an internal control from 20 subjects

and NQO1. The relative levels of gene expression were calculated after normalization to an internal control. In each case, control expression (that seen in cells from lavages after challenge with saline) of the genes was given an arbitrary figure of 1.0 and relative expression calculated with reference to baseline. Figure 1 shows that expression of GSTP1 increased 24 hours after challenge with DEP. For nearly all subjects, there is a dose-response relationship between gene expression and the dose of DEP used in the nasal challenge. Similar results were observed in response to DEP challenge in expression of GSTM1, NQO1 and HO-1. While there was substantial inter-individual variation in the expression of any single enzyme, there was a very significant correlation between expression of all four enzymes, suggesting they are closely regulated. Cellular inflammation was measured in nasal lavages performed 24 hours after DEP challenge. As expected, there was a strong correlation between total cell number and the dose of DEP used in the nasal challenges. Moreover, total cell numbers were inversely correlated with expression of GSTP1 ($p=0.03$) and GSTM1 ($p=0.04$). DEP enhanced production of IL-8, TNF-α and GM-CSF in a dose-dependent fashion. Higher DEP challenge dose concentrations were

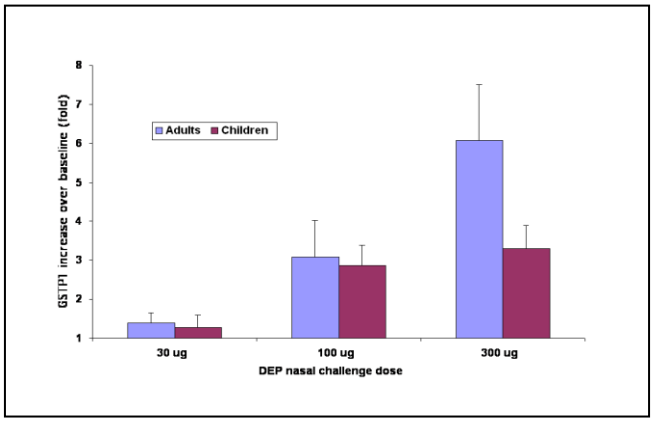

Figure 2 GSTP1 response to DEP in adults vs. children

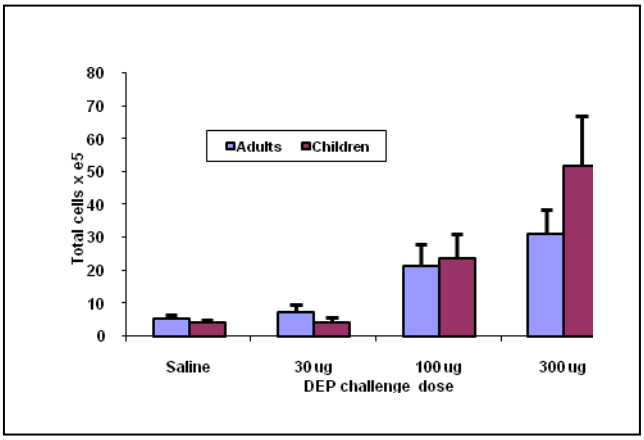

Figure 3 Cellular response to DEP in adults vs. children

associated with increased levels of chemokines.

We expanded these studies and completed similar challenges in 20 children. In adults, DEP induced expression of GSTP1 in a dose-dependent fashion. With increasing concentrations of DEP challenge, there were higher levels of GSTP1-relative gene expression. Cellular infiltration was inversely correlated with GSTP1 enzyme gene expression. Increased levels of GSTP1 were associated with lower cell count numbers. In children, the degree of cellular infiltration also correlated with dose of nasally administered DEP challenge. Higher concentrations of DEP elicited a larger number of total cells recovered from nasal lavage fluid obtained 24 hours after DEP exposure. However, as compared to adults, this effect in children was more robust at the DEP challenge of 300 µg. In these children, DEP also induced expression of GSTP1. At DEP concentrations of 30 and 100 µg, there were higher levels of GSTP1-relative gene expression. However, *GSTP1-relative gene expression for the DEP nasal challenge of 300 µg was decreased in children as compared to adults.* Similar results were seen with the other three measured Phase II enzymes.

These results suggest that children appear to be more vulnerable to the adverse effects of oxidant pollutants, and they support the concept that the potential of an individual to mount a Phase II antioxidant defense may regulate the development of acute and chronic airway inflammation. We extended these studies to test whether *in vitro* Phase II enzyme expression can predict *in vivo*

inflammatory responses to DEP. We recruited 20 allergic but otherwise healthy volunteers and obtained blood samples. We purified peripheral blood mononuclear cells (PBMNCs) from the subjects and stimulated the cells with 10 ug/mL of DEP in 1mL plates. After incubation for 24 hours, glutathione-S-transferase (GST) activity was measured by following the conjugation of 1mM 1-chloro-2,4,dintrochlorobenzene (CDNB) with 1mM GSH in 200mM sodium phosphate buffer as measured at 340nm using a spectrophotometer over time. Enzyme activity was expressed as millimoles of CDNB conjugated per minute per milligram of cytosolic protein. The subjects were then challenged intranasally with 300ug of DEP with nasal lavages performed prior and 24 hours after challenge.

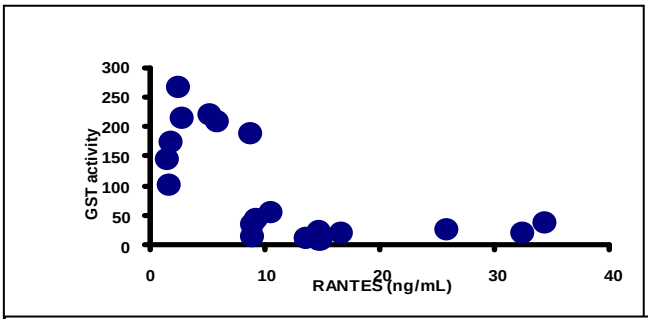

Figure 4 *In vitro* GST activity predicts *in vivo* inflammatory responses

As seen in Figure 4, *in vitro* GST activity predicted *in vivo* inflammatory responses. The population could be divided into two populations: the first as those with a GST activity above 100 which had low or minimal inflammatory responses following DEP challenge. In this population (n=8), cell influx into the nose was limited and production of pro-inflammatory cytokines (GM-CSF, IL-1beta) and chemokines (RANTES, IL-8) was not statistically different after DEP challenges vs. baseline levels. The second population (n=12) had a GST activity under 60 and was characterized by a significant or very robust second inflammatory response following DEP challenge. In this population, there was a statistically significant increase in pro-inflammatory cytokines and chemokines after challenge. In addition, GST activity in this population was inversely proportional to cell numbers or RANTES production. Determining GST activity from blood cells may be a useful test to determine susceptibility to pollutants.

Aim 2

We exposed 20 healthy and 20 asthmatic subjects to diesel exhaust to study the effect of Phase II expression on lower airway responses. We could reproducibly produce a diesel particulate exposure level that was within 8% of the target level every time. These diesel particles are chemically and physically identical to diesel particles encountered in ambient air. Diesel exhaust resulted in increased expression of all four sentinel Phase II enzymes (GSTM1, GSTP1, HO-1 and NQO1) tested in cells recovered from sputum induced 24 hours after exposure to 2 hours of diesel exhaust (100 µg/m3). IL-8 levels in the sputum of subjects were significantly inversely correlated with Phase II expression. This increase was observed in both healthy and asthmatic subjects. There was wide heterogeneity in responses to DEP between subjects. While no enhanced inflammation was observed in any of the healthy subjects, four out of the twenty asthmatic subjects demonstrated a robust inflammatory response to DEP but not filtered air.

Aim 3

We have previously shown 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. We tested whether this same reagent could block DEP-mediated adjuvant events *in vivo* in a murine model.

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 min), DEP (1 hr) or OVA followed immediately by DEP for ten consecutive days. Mice were administered either vehicle (corn oil) or sulforaphane (4.5 μmol/mouse/day) by gavage (0.2 ml) for one week prior to the commencement of exposures up until two days after the last exposure. As expected, in the untreated group, IgG1 levels were significantly higher in mice who received both DEP and OVA than in those who were exposed to OVA alone. However, administration of sulforaphane completely ablated the adjuvant effects of DEP.

We then examined the responses of the airway epithelial cell line BEAS-2B and primary normal human bronchial epithelial cells upon treatment with sulforaphane and Phase II enzymes followed by stimulation with diesel extract (0-25 μg/ml). As expected, sulforaphane upregulated the expression of endogenous antioxidant enzymes in bronchial epithelial cells. Whereas diesel extract stimulated the production of IL-8, GM-CSF, and IL-1β from normal human bronchial epithelial cells, pre-treatment with sulforaphane for 24 hours inhibited diesel-induced cytokine production in a dose-dependent fashion. These studies suggest that sulforaphane treatment can prevent the production of pro-inflammatory cytokines in respiratory epithelial cells *in vitro*. Previously, we reported that individuals who lack the ability to make the Phase II enzyme GSTM1 are at increased risk for the pro-inflammatory effects of DEP, and we have shown that enhancement of Phase II enzymes with sulforaphane can inhibit the production of pro-inflammatory cytokines in respiratory epithelial cells *in vitro*. In order to determine whether GSTM1 itself is important in the regulation of inflammatory response to pollutants, we used siRNA to "knock down" the GSTM1 gene in bronchial epithelial cells. Expression could be reduced by more than 90% using this methodology. Knockdown of GSTM1 augmented DEP induced cytokine production in these cells. Thus, IL-8 levels were almost three-fold higher in cells where GSTM1 expression was reduced, compared to sham-treated cells.

Finally, in a placebo-controlled dose escalation trial to investigate the *in vivo* effects of sulforaphane, we demonstrated that consumption of oral sulforaphane contained in broccoli sprouts homogenate (BSH) can induce a potent increase in antioxidant Phase II enzymes in airway cells. RNA expression for GSTM1, GSTP1, HO-1 and NQO1 was measured in nasal lavage cells by RT-PCR before and after sulforaphane dosing. Increased Phase II enzyme expression occurred in a dose-dependent manner with maximal enzyme induction observed at the highest dose of 200 g broccoli sprouts prepared as BSH. Significant increases were seen in all sentinel Phase II enzymes RNA expression compared to baseline. Phase II enzyme induction was not seen with ingestion of non-sulforaphane containing alfalfa sprouts. These findings suggest enhancement of Phase II enzyme expression as a novel therapeutic strategy for oxidant-induced airway disease.[25]

Conclusions

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. A principal finding of our results is the discovery that children have enhanced inflammatory responses to the model pollutant DEP and that this seems to be related to their reduced capacity to make a cytoprotective Phase II enzymes response. Our studies illuminate why there may be increased susceptibility of certain vulnerable individuals and populations (such as children) to oxidant

pollutants and suggest that increasing the body's Phase II responses either by therapeutic or dietary means may counteract this effect. Moreover, the discovery that *in vitro* GST expression is associated with *in vivo* inflammatory responses provides the potential to develop a diagnostic test for susceptibility to oxidant pollutants.

Project 3: Air Pollution, Exhaled Breath Markers and Asthma in Susceptible Children

Hypotheses

1. High ambient air pollution exposure is associated with chronic airway inflammation in children as indicated by elevated eNO, a marker of airway inflammation and oxidative/nitrosative stress.
2. Children's susceptibility to airway inflammation and oxidative/nitrosative stress from ambient air pollution varies by NOS1, NOS2 and NOS3, GSTM1, GSTP1, NQO1, and HO-1 genotypes.
3. Children with chronic airway inflammation as indicated by elevated eNO are at increased risk for new onset asthma.

Specific Aims

1. Collect eNO from 3000 children in the ongoing AIR study cohort.
2. Genotype the cohort of 3000 children for functional polymorphism/haplotypes in the NOS1, NOS2 and NOS3, GSTM1, GSTP1, NQO1, and HO-1.

To assess Hypotheses 1 and 2:

3. To use a multilevel design to determine the relationship between levels of eNO with short- and long-term air pollution exposures and to assess the effects of genetic variation in NOS1, 2, and 3 on these relationships using data collected in SA1, SA2 and air pollution exposure estimates from the ongoing cohort study.

To assess Hypothesis 3:

4. To determine the risk for new onset asthma in children with high levels of eNO using data collected in SA1 and in the ongoing prospective cohort study of incident asthma.

Accomplishments

In the past five years, we assessed three hypotheses based on a biological model for the oxidative stress and inflammatory pathways involved in the pathogenesis of adverse effects of air pollution: (1) High ambient air pollution exposure is associated with chronic airway inflammation in children as indicated by elevated exhaled NO (eNO), a marker of airway inflammation and oxidative/nitrosative stress; (2) Children's susceptibility to airway inflammation and oxidative/nitrosative stress from ambient air pollution varies by NOS1, NOS2 and NOS3, GSTM1, GSTP1, NQO1, and HO-1 genotypes; and (3) Children with chronic airway inflammation as indicated by elevated eNO are at increased risk for new onset asthma.

We first investigated whether high ambient air pollutant exposures were associated with elevated eNO (marker of inflammation) in more than 2,700 children. We found that exposures to particulate matter less than 2.5 microns in diameter ($PM_{2.5}$) mass concentration (two to seven-day average prior to the test) were associated with increased eNO. In order to investigate the second hypothesis, we assessed whether specific genetic variants were associated with airway inflammation (elevated eNO) and children's susceptibility to airway inflammation from ambient

air pollution. We found strong evidence that variation in several genes on the nitric oxide (NO) synthesis pathway, including NOS2A and ARG2, are associated with eNO, susceptibility to air pollution, risk of new onset asthma and lung function growth. Finally, in order to evaluate hypothesis 3, we investigated whether elevated exhaled NO at baseline is associated with new onset asthma during the follow-up period. We determined that children with chronic airway inflammation as indicated by elevated eNO are at increased risk for new onset asthma.

Conclusions

Taken together, these findings support the hypothesis that ambient PM produces inflammation and oxidative/nitrosative stress in the airways and provide evidence that airway inflammation/nitrosative stress contributes to asthma pathogenesis and abnormal lung function development. Furthermore, these findings indicate that variants in genes involved in NO production pathways may affect susceptibility to the adverse effects of air pollution. Based on preliminary data, studies of genes and pathways involved in regulating inflammatory responses are likely to provide crucial information needed to understand the role of the interrelated processes of oxidative/nitrosative stress on inflammation in respiratory disease pathogenesis.

SUMMARY OF KEY RESEARCH FINDINGS FROM THE PREVIOUS CYCLE

The CEHC has yielded a wealth of data on the acute and chronic respiratory effects of air pollutants; gene-environment interactions; host susceptibility to air pollutants; novel spatial modeling approaches and methods; and exposure assessment methodology. The interdisciplinary nature of this Center has made it possible to develop an integrated program that is synergistic and provides a larger return on investment than would a single investigator model. In this section, we briefly summarize some of the key research findings.

Health Effects of Air Pollution and Tobacco Smoke Exposures

1. Current levels of air pollution have chronic, adverse effects on lung development in children from the age of 10 to 18 years, leading to clinically significant deficits in attained FEV_1 as children reach adulthood.[8]
2. Respiratory health in children is adversely affected by local exposures to outdoor NO_2 or other freeway-related pollutants.[26]
3. Residential traffic exposure is associated with deficits in lung function growth.[27]
4. Residential traffic exposure is associated with prevalent asthma, lifetime asthma and wheezy phenotype.[3, 28]
5. New onset asthma in primary school children is independently associated with local traffic-related pollution near homes and near schools.[29-30]
6. Markers of traffic-related air pollution are associated with the onset of asthma, providing further evidence that air pollution exposure contributes to new cases of asthma.[31-32]
7. On-road commuting exposure to air pollution increases the risk of asthma.[33]
8. Maternal and grandmaternal smoking during pregnancy may increase the risk of childhood asthma.[34]
9. Regular cigarette smoking increases the risk for new onset asthma among adolescents, especially among those exposed to maternal smoking during the *in utero* period.[35]

Susceptibility

1. Variation in several genes in the nitric oxide (NO) synthesis and inflammatory pathways, including NOS2A, ARG2, and 5-LO, are associated with eNO, susceptibility to air pollution, and asthma pathogenesis.[36-39]
2. Variants in cytokine genes are associated with exhaled NO and incident asthma [40-41]
3. The tumor necrosis factor (TNF)-308 GG genotype may have a protective role in asthma pathogenesis depending on airway oxidative stress levels.[42]
4. In children with at least one copy of the TNF-308 A variant, exposure to two or more household smokers is associated with a two-fold risk of a school absence due to respiratory illness (RI) and a four-fold risk of lower RI-related school absence compared with unexposed children with the TNF-308 GG genotype.[43]
5. Gluthathione-s-transferase M1 and PI (GSTM1 and GSTP1) modify the adjuvant effect of diesel exhaust particles on allergic inflammation.[17]
6. Certain variants in intercellular adhesion molecule-1 (ICAM-1) are associated with reduced risk for asthma. Differences in associations of asthma risk with ICAM-1 were found between African-Americans and non-Hispanic and Hispanic whites.[44-45]
7. High microsomal epoxide hydrolase (mEH) activity is associated with increased asthma risk and children with both high mEH activity and GSTP1 105Val are at the greatest risk.[46-47]
8. The clara cell secretory protein gene (CC16) variant allele at position 38 is associated with susceptibility to asthma and wheezing in African-Americans and the risk of early onset asthma among non-Hispanic Whites with a family history of asthma.[48]
9. Genes in glutathione regulation alter the effect of air pollution on lung function growth[49] and asthma.[50]
10. Dog ownership enhances symptomatic responses to air pollution in children with asthma.[51]
11. Decreased airway flows predict new onset asthma in preadolescent and adolescent children.[51-52]
12. Children with the val105 variant of GSTP1 may be protected from the increased risk of asthma associated with exercise, especially in high ozone communities.[53]
13. Functional promoter variants in HMOX-1 are associated with a reduced risk for new-onset asthma among non-Hispanic whites; this protective effect is largest in children residing in low-ozone communities.[54-55]
14. Genetic variation across the GST mu locus is associated with eight-year lung function growth.[56]
15. Children of mothers who smoked during pregnancy with variation in GSTM2 have lower lung function.[56]
16. Genetic variants in both the promoter and coding regions of the GSTP1 locus may contribute to the occurrence of childhood asthma and wheezing and may increase susceptibility to adverse effects of tobacco-smoke exposure.[57]
17. A positive association is seen between community-level socio-economic position and prevalent and incident childhood asthma, suggesting a significant role for environmental factors in the etiology of this disease.[58-59]
18. Parental stress increases the risk of childhood wheeze among children with no parental history of asthma, especially among boys.[60]
19. Parental stress and low socioeconomic status increase the risk of childhood wheeze and asthma associated with traffic-related air pollution.[61]

Mechanism

1. Exhaled NO is a useful biomarker for airway inflammation in large population-based studies.[62-64]
2. Exposure to particulate matter less than 2.5 microns in diameter ($PM_{2.5}$) mass concentration (two to seven- day average prior to the test) is associated with increased exhaled NO.[65]
3. Children with chronic airway inflammation, as indicated by elevated eNO, are at increased risk for new-onset asthma.[66]
4. Primary allergic sensitization may be prevented by initial high levels of respiratory allergen exposure through induction of a modified, nonallergic immune response.[67]
5. Evidence from controlled chamber experiments shows that secondhand smoke can exacerbate allergic responses in humans.[68]
6. A natural protective mechanism in B cells from oxidant pollutants, such as diesel particles, is the expression of phase II enzymes through induction of antioxidant response elements.[23]
7. Induction of phase II enzymes by the chemical sulforaphane can block DEP-induced enhanced IgE production in B cells and DEP-induced proinflammatory cytokine production in epithelial cells.[69]
8. Pretreatment with sulforaphane inhibits diesel-induced production of IL-8, granulocyte-macrophage colony-stimulating factor, and IL-1beta from primary human bronchial epithelial cells, demonstrating that sulforaphane can mitigate the effect of diesel in respiratory epithelial cells.[24]
9. A placebo-controlled dose escalation trial demonstrates that sulforaphane from broccoli sprouts induces a potent increase in antioxidant Phase II enzymes in airway cells and suggests enhancement of Phase II enzyme expression as a novel therapeutic strategy for oxidant induced airway disease.[25]

New Methodology

1. Offline eNO field measurements can predict online eNO with concurrent ambient NO measurements.[70-72]
2. Field-based extended NO testing of children yields useful information about NO at different levels of the respiratory tract, not obtainable from conventional eNO measurement [73]
3. The development of models to assess air pollution exposures within cities for assignment to subjects in health studies augments the field of exposure assessment and may help to reduce scientific uncertainties that now impede policy intervention aimed at protecting public health.[74]
4. Methods were developed to optimally locate a dense network of monitoring stations representing land use, transportation infrastructure, and the distribution of at-risk populations; this has widespread applicability for the design of pollution monitoring networks, particularly for measuring traffic pollutants with fine-scale spatial variability.[75]
5. Residential ozone concentrations may be over- or underestimated by measurements at a community monitor, depending on the variation in local traffic in the community.[76]
6. Statistical methods have been developed related to the general multilevel modeling paradigm, with a focus on flexible modeling techniques for nonlinear lung function trajectories in children and their relationship to air pollution. The models address many issues, including ecologic inference, multi-pollutant and subgroup analysis, simultaneous modeling of several outcomes, and exposure measurement error.[77]
7. A testing strategy called the "focused interaction testing framework" (FITF) was developed to identify susceptibility genes involved in epistatic interactions for case-control studies of candidate genes. In CHS data, FITF identified a significant multilocus effect between NQO1,

MPO, and CAT, three genes involved in the oxidative stress pathway. In an independent data set, these three genes also show a significant association with asthma status.[78]

8. For analysis of a single candidate gene, the SNP interaction model with phase information (SIMPle) model can be used to identify important SNPs and underlying haplotype structures across a variety of causal models and genetic architectures.[79]
9. A two-step approach was developed to test association of disease with multiple single nucleotide polymorphisms (SNPs) within a candidate locus. The first step uses principal components (PCs) analysis to compute combinations of SNPs that capture the underlying correlation structure within the locus. The second step uses the PCs directly in a test of disease association.[80]
10. A two-step analysis of genome-wide association study data aimed at identifying genes involved in a gene-environment interaction was developed. The procedure complements standard screening for marginal genetic effects and has the potential to uncover novel genetic signals.[81]

Community Outreach and Translation

1. Traditional approaches to the calculation of attributable risk may underestimate the health impact of long-term environmental or other exposures that produce both chronic and acute disease.[82]
2. Community-based quantitative risk analyses can improve our understanding of health problems and help promote public health in transportation planning.[83-84]
3. As ports and goods movement activity expands throughout the United States, outreach efforts in the Center have made health and community impacts a more central part of policy discussions.[85-88]
4. The large population of children exposed to high levels of outdoor air pollutants and the substantial risks for adverse health effects presents unexploited opportunities to reduce the burden of asthma.[89]

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