EGR-1 IS ESSENTIAL FOR INDUCED AIRWAY HYPER-RESPONSIVENESS IN MICE

ES Silverman, GT De Sanctis, A Jiao, KH Haley, J Boyce, JD Parvin, J Milbrandt, T Collins, JM Drazen. Pulmonary and Critical Care Division, Dept of Medicine, Dept of Pathology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA and Dept of Pathology and Internal Medicine, Washington University School of Medicine, St. Louis, MO

Early Growth Response Protein (Egr-1) is a sequence specific DNA-binding protein implicated in the transcriptional regulation of 5-Lipoxygenase (5-LO) and other genes (Silverman et al., AJRCMB, 1998). Egr-1 binds to the G+C-rich region of the 5-LO core promoter and up-regulates promoter activity *in vitro* (In et al., JCI, 1997). To establish a causal relationship between Egr-1 *trans*-activation, 5-LO gene expression and murine models of asthma, we examined Egr-1 knock-out (KO) mice in an ovalbumin (OVA) induced model of airway inflammation and bronchoreactivity. In response to methacholine challenge, OVA sensitized and challenged Egr-1 KO mice were hypo-responsive ED_{150}= 2.01 ± 0.10, compared with identically treated wild type control mice, ED_{150}= 2.44 ± 0.06, (P< 0.01). These data suggest that Egr-1 is necessary for the full expression of enhanced airway reactivity after allergen stimulation in mice. We speculate that the observed differences in airway reactivity are due to differences in the transcription of 5-LO and the subsequent production of leukotrienes. The Egr-1 transcriptional pathway may be activated in asthma.

Supported by: K08HL03827, HL36110 and the ALA

This abstract is funded by:

ASSESSMENT OF OCCUPATIONAL EXPOSURE RISKS USING JOB / INDUSTRY TITLES IN ASTHMA EPIDEMIOLOGY - METHOD DEVELOPMENT AND APPLICATION IN THE EGEA STUDY.

SM Kennedy, N Le Moual, D Choudat, E. Kauffmann, INSERM U472, Villejuif, France.

To determine if job and industry titles, coded to international codes, could provide sufficient information to characterise occupational asthma (OA) risk in population based studies, we developed and tested a method for assigning subjects to OA asthma risk groups. First, we created a matrix to link job and industry codes to one or more of 19 risk groups (14 'high risk' and 5 'low or moderate risk') classified by known OA hazards (method 1). Second, we modified individual risk group assignments where necessary after examining brief job and industry descriptions (text, not codes) from the questionnaires, with the aid of computer sorting (method 2). We applied these methods to data from the EGEA study of risk factors for asthma (a case-control and family study). Among the 1121 adults who had ever held a job (175 asthma cases from chest clinics, 286 controls, and 660 family members of cases), 280 changes of risk group assignment occurred, after applying method 2 ; with 21 persons changing from a 'high risk' classification to 'low or moderate risk', and 7 from 'low/moderate' to 'high risk'. Comparing cases and controls, using risk groups from method 1, neither the combined high risk group, nor any of the 14 specific risk groups showed a significantly increased asthma risk. With method 2, high risk exposure was significantly related to asthma (OR : 1.9, 95%CI : 1.2, 3.2) and OR's >3 were seen for metal working fluid, metal fumes, agricultural exposures, and cleaning agents. We conclude that job and industry codes used in combination with inspection of brief job and industry descriptions, by researchers with some experience in occupational asthma exposure risks, can be sufficient to characterize some OA risks, but that codes alone may not be specific enough for this task.

This abstract is funded by: Convention INSERM/MSD and Ministry of Employment

ASTHMA EXACERBATED BY WORKPLACE EXPOSURES

PK Henneberger, R Deprez, NL Asdigian, LC Oliver. Div. of Resp. Disease Studies, NIOSH, Morgantown, WV and Public Health Research Institute, Portland, ME, USA.

Few studies have addressed the exacerbation of asthma by workplace exposures. As part of a population-based study of asthma in five hospital service areas in Maine, subjects completed a telephone questionnaire. There were 490 adult participants (aged 18 to 65 years) who were employed within the past year. A total of 80 (16.3%) were identified as asthma cases, including 45 (9.2%) with physician-diagnosed asthma and another 35 (7.1%) with undiagnosed asthma who were identified by responding affirmatively to at least 4 of 9 questions that asked about cough, wheeze, chest tightness, and difficulty breathing. Of the 80 asthmatic subjects, 17 (21.3%) reported that their coughing or wheezing was worse at work, including 7 of the diagnosed cases (15.6%) and 10 of the undiagnosed cases (28.6%). Asthmatics with workplace exacerbation were similar to other asthmatics with respect to gender, smoking, marital status, and education level. However, the work-exacerbated asthmatics were somewhat older and had worked longer in industries designated a priori to be at high risk for asthma. When a report of coughing or wheezing worse at work was modeled for asthmatics using logistic regression, and controlling for age, gender, and smoking, an elevated odds ratio was observed for subjects who had worked over 8 years in a high-risk industry (OR=5.7, 95% CI 1.1-30.4, p=0.04). Other analyses limited to the physician-diagnosed cases suggested that work-exacerbated asthmatics required more medical care and were more limited in daily activities, but the small number of subjects precluded firm conclusions. These findings suggest that the exacerbation of asthma by workplace exposures is common and might have serious consequences.

American Lung Association of Maine and CDC

This abstract is funded by:

OUTCOME OF ASTHMA INDUCED BY ISOCYANATES.

C.E. Mapp[1], M. Saetta[1], P. Maestrelli[1], R. Benzon[1], V. Pozzato[1], G. Mastrangelo[1], L.M. Fabbri[2]. University of Padova (1) and of Ferrara (2). Italy.

The study population was composed of 48 subjects with isocyanate-induced asthma. At diagnosis and at follow-up examination, respiratory symptoms, persistence of exposure to isocyanates, smoking, therapy, and lung function have been investigated. The subjects were examined at different intervals (3-14 times) up to 130 months. To analyze changes in dependent variables (i.e. FEV_1 and PD_{20} FEV_1 methacholine), we used a longitudinal linear model (unbalanced repeated measures model) which takes into account the effect of both risk indicators and confounding factors. We found that airway responsiveness to methacholine was a sensitive indicator of cessation or persistence of exposure to isocyanates. The decrease in airway responsiveness to methacholine was slow and gradual and continued after 96 months from the cessation of exposure. The worst outcome in airway responsiveness to methacholine was associated with atopy. FEV_1 was a less sensitive indicator, being its changes related to cigarette smoking rather than to exposure. Our findings indicate that PD_{20} FEV_1 methacholine is a sensitive parameter to evaluate the effects of the exposure to isocyanates. Moreover, these results suggest that the persistence of exposure and presence of the atopy are unfavourable prognostic factors for isocyanate-induced asthma.

Supported by grants from MURST, A.R.C.A., A.S.T.M.P., Ferrarricerche and Arcispedale Sant'Anna, Ferrara.

This abstract is funded by: