ENVIRONMENTAL POLLUTION IMPACT ON THE RESPIRATORY SYSTEM OF LIGNITE MINERS

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The aim of the study is the research of the diachronic impact of environmental pollution on the respiratory system of lignite miners at Ptolemaida's mines. Cases of 193 workers (Group A) living permanently in Eordea valley, 214 (Group B) living outside the Eordea valley were studied during Phase I and then re-examined after three years (Phase II). These cases were compared to those of 58 white-collars living in Ptolemaida (Group C) and of 56 living in the region of Grevena (Group D). The study included complete spirometry and ergospirometry, rhinomanometry as well as chest and paranasal cavities X-rays. The spirometry and ergospirometry findings presented no considerable differences neither in the 4 groups nor between the phase I and II of the study. This is due to the short interval of re-examination since the impact of smoking was not detectable to the functionality of the lungs. The main problems were detected in the upper airways. Very high rate of severe rhinitis and atrophic rhinitis was detected both among workers and subjects living in Ptolemaida who participated as controls. A considerable improvement was obvious at phase II for subjects submitted to a local treatment with steroids. From the X-rays, hypertrophy of nasal turbinates-cartilage ar polyposis was observed as follows: Group A 54%, Group B 48.1%, Group C 46.5% a. Group D 24.3%. The findings related to the upper respiratory system are due tr the excessive air suspended particles pollution in the region and particularly to chromium nickel and cadmium found at high concentrations in the air suspende. d. Considerable association between the total air flow in the nose and the intere flow ($p<0.01$) was detected. In conclusion, the persons working in mines wit air suspended particles pollution, apart the other examinations, they should be to rhinomanometry and to X-ray imaging of paranasal cavities.

NOTE

MATRIX METALLOPROTEINASE INDUCTION IN FIBROSIS AND FIBROTIC NODULE FORMATION DUE TO SILICA INHALATION

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Matrix Metalloproteinases (MMP) are the enzymes that initiate degradation of collager. We examined the role of MMPs during alveolar wall fibrosis and fibrotic nodule formation due to silica exposure. Rats were exposed to 15 mg/m^3 silica or filtered air for 5 days/week, 6 hours/day. Lungs were preserved by intra-tracheal instillation of fixative at 40, 60, 79 and 116 days of exposure. Additional rats were sacrificed for collagenase and zymographic assays. Tissue sections were processed for Sirius Red staining of collagen and immunohistochemistry detection of Stromelysin (MMP-10), Gelatinase A (MMP-2), Tissue Inhibitor of Metalloproteinase (TIMP-1) and TGF-β. The number of fibrotic nodules were determined by morphometric analysis. Fibrotic nodules were defined by a collagenous core and a bounding cell layer detached from the alveolar wall. At 79 and 116 days, exposed lungs showed an increase of collagen in alveolar walls and fibrotic nodules. Simultaneously, the collagenase assay and gelatin zymography showed an increase in MMP activity over filtered air controls. The number of nodules per lung in silica exposed groups were 8.6 ± 6.2, 37.5 ± 11.1, 66.4 ± 2.3 and 183.0 ± 15.2 at 40, 60 79 and 116 days respectively (mean±SE,n=5). No nodules were seen in the control lungs. MMP-2 and TGF-β were significantly elevated in alveolar macrophages throughout the lung. In addition to being elevated in alveolar macrophages, Stromelysin was seen in interstitial cells located in fibrotic nodules. TIMP-1 expression was not significant. In summary, MMP activity was upregulated at the initial stages of exposure and progressively increased during ensuing fibrotic responses of the lungs to silica. Early expression of Stromelysin was found in fibrosing alveolar walls and in the core of fibrotic nodules. These results demonstrate Stromelysin as an early marker of silicosis.

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ROLE OF INTERFERON-GAMMA IN MURINE BRONCHUS-ASSOCIATED LYMPHOID TISSUES INDUCED BY SILICA.

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Silicosis is a disabling occupational lung disease characterized by the development of fibrotic nodules in the lung. To elucidate the pathogenetic role of interferon(IFN)-gamma in silicosis, we studied silica-induced lung disease in IFN-gamma deficient mice. Mice were treated intratracheally with either a single fibrogenic dose of silica or an equivalent volume of saline and sacrificed after 21 days. Total cell counts in bronchoalveolar lavage fluids increased in silica-treated group compared with saline-treated group, but there was no difference between IFN-gamma deficient mice and wild controls. In addition, silica instillation induced severe lung inflammation and fibrosis in both IFN-gamma deficient and sufficient groups, and morphometric estimation for fibrotic lesions within the lung did not show any difference between the two groups. Hydroxyproline assay confirmed this biochemically. However, the average size of bronchus-associated lymphoid tissues (BALT) treated with silica was significantly larger in the lung of IFN-gamma deficient mice ($15.7\pm1.9 \times 10^{-3}$ mm^3) than that in the lung of the wild-type ones ($3.7\pm0.7 \times 10^{-3}$ mm^3), which were calculated assuming a spherical shape. These results showed that IFN-gamma has an inhibitory effect on the formation of BALT induced by intratracheal instillation of silica, suggesting that IFN-gamma plays an important role in the local mucosal immune response in vivo.

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SERUM SP-A, SP-B, & CC16 AS MARKERS OF TOBACCO-INDUCED LUNG EPITHELIAL DAMAGE

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Introduction: Cigarette smoking increases lung epithelial permeability both acutely through smoke-mediated release of vasoactive neuropeptides (tachykinins) from sensory nerves in the airways and chronically through early destruction of connective tissue in the alveoli. We have shown increased leakage of surfactant proteins-A and -B (SP-A, SP-B) and Clara cell secretory protein (CC16) from the airspaces into the circulation in a range respiratory conditions. Therefore, we investigated whether serum levels of these proteins might provide a useful index of lung epithelial damage associated with tobacco smoking. **Methods:** All proteins were measured in 53 healthy smokers (42 years [21 to 60]; mean [range]) and 68 age and gender matched non-smokers subjects (44 years [18 to 60]) by immunoassays as described before*.

...lts:	CC-16 (ng/ml)	SP-A (ng/ml)	SP-B (ng/ml)
...ers	11.4 [4.7 to 22.6]	313 [93 to 893]	2,585 [1,197 to 4,873]
	9.1 [2.4 to 21.4]	330 [143 to 1,051]	3,838 [1,589 to 11,325]

...reased serum CC-16 ($p< 0.0015$) but increased SP-B ($p < 0.0001$) in a ...ted to pack-years ($rs = 0.53$, $p < 0.001$). **Conclusion:** Smoking increases ...pillary permeability in a dose related fashion and is toxic to Clara cells. ...ently, the CC16/SP-B ratio may prove a powerful index of tobacco smoke-mic...es lung epithelium damage.

*Doyle IR, Hermans C, *et al.* Am J Respir Crit Care Med 1998;158:1528-35.

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ACTIVATION OF EXTRACELLULAR SIGNAL-REGULATED KINASES AFTER INSTILLATION OF DIFFERENT COAL MINE DUSTS AND SILICA IN RAT LUNG EPITHELIUM.

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Background: Animal studies in rats have shown an increase in epithelial cell proliferation, a well-known preneoplastic lesion in the lung after instillation of different coal mine dusts (CMD). There is also epidemiological evidence that lung cancer in coal miners is increased. We hypothesized that the effect in animals might be caused by a persistent activation of kinases involved in the upregulation of transcription factors important in cell proliferation. **Methods:** Femal Wistar rats were intratracheally instilled with multiple doses of different coal samples (60 mg), quartz DQ12 (5 mg), or 0.4 mL 0.9% saline solution containing 0.5% Tween 80. After 126 weeks, lung tissue sections were examined for activation of extracellular signal regulated kinases (ERKs)1/2 using an antibody against the phosphorylated form of the protein. **Results:** Whereas in the control animals only some epithelial cells show a positive signal we found a strong activation of ERKs1/2 in the poorly soluble dust treated lungs. The activated cells (alveolar and bronchiolar epithelial cells as well as macrophages) were usually observed near origins where dust was located. **Conclusions:** The results suggest that ERKs are an important signal transduction pathway for particle induced pulmonary effects in the rat.

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PROLIFERATION AND ACTIVATION OF EXTRACELLULAR SIGNAL-REGULATED KINASES AFTER TREATMENT WITH DIFFERENT POORLY SOLUBLE PARTICLES IN A MURINE ALVEOLAR TYPE II EPITHELIAL CELL LINE

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Studies in rats have shown an increase in epithelial cell proliferation, a possible preneoplastic change in the lung after instillation of different coal mine dusts (CMD). Alveolar type II epithelial cells are considered as the main precursor cells for these lesions, but until now the mechanisms of proliferation are unclear. There is some evidence for the involvement of reactive oxygen species (ROS) in stimulation of cell signaling cascades that trigger transcriptional events important in proliferation. Cell cycle kinetics, cell signaling and gene expression were investigated after exposure of murine C10 cells with CMD of high or low quartz content, DQ12 silica, and glass beads as a nonpathogenic particle control. To determine activation of extracellular signal-regulated kinases (ERKs 1/2), we investigated levels of phosphorylated proteins by Western blotting. Using a ribonuclease protection assay, increased mRNA levels of *fos* and *jun* family members were seen in response to DQ12 and CMD of high quartz content. Flow cytometry showed increased numbers of cells in S phase by DQ12 and CMD. Increased phosphorylation of ERKs 1/2 was seen in DQ12- and CMD- exposed cells. The use of a hydroxyl radical scavenger blocked the induction of proliferation by DQ12 and CMD and the phosphorylation of ERKs 1/2, indicating a role for ROS in the cell signaling process after particle treatment.

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