(IM) in airway epithelium. Conducting airways were microdissected and analyzed for expression of the rat mucin gene rMuc5AC. Endotoxin caused a dose-dependent increase in BAL neutrophils that was increased 2-fold in ozone-exposed rats given 20 μg endotoxin. Mucin glycoprotein 5AC was elevated in BAL from rats exposed to 20 μg, but not 2 μg endotoxin. Exposure to ozone alone did not cause mucus hypersecretion, but ozone potentiated secretion induced by 2 or 20 μg endotoxin. Airways of rats exposed to air or ozone alone had scant amounts of IM. Endotoxin instillation induced a dose dependent increase in IM in airway epithelium that was significantly increased (2-fold) in rats coexposed to ozone. Expression of rMuc5AC was induced by 2 and 20 μg endotoxin, and was further increased in ozone-exposed rats instilled with 20 μg endotoxin. These results demonstrate that ozone exposure potentiates inflammatory and epithelial responses induced by endotoxin in rat pulmonary airways. Research supported by NIH Grant HL59391

935 ACUTE INFLAMMATION AND RECOVERY IN RATS AFTER INTRATRACHEAL INSTILLATION OF A 1→3-β-GLUCAN (ZYMOSAN A).

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1→3-β-Glucans derived from the inner cell wall of yeasts and fungi have been implicated in organic dust toxic syndrome. However, animal studies report conflicting results concerning the inflammatory potency of 1→3-β-glucan. In this experiment, we assessed the pulmonary reaction of rats to 1→3-β-glucan (zymosan A) exposure. Male Sprague-Dawley rats were exposed *via* intratracheal instillation (IT) to zymosan A (dose range: 0-5 mg/kg body weight). Rats were sacrificed 1-7 days post-exposure and the following pulmonary responses monitored: (1) breathing frequency, (2) differential cell counts of bronchoalveolar lavage (BAL) cells, (3) chemiluminescence (CL) as a measure of alveolar macrophage activation, (4) nitric oxide production by alveolar macrophages, and (5) albumin and (6) lactate dehydrogenase (LDH) levels in the first lavage fluid. Upon challenge with zymosan A, rats exhibited a dose-dependent pulmonary response at one day post IT which was significantly higher than the control level at a dose of 1 mg/kg body weight. Post-IT breathing frequencies and polymorphonuclear leukocytes (PMN) obtained by BAL both correlated very well with zymosan A concentration (r^2 = 0.95 and 0.99, respectively). Albumin and LDH levels of the acellular BAL fluid correlated (r^2 = 0.80) with the dose of zymosan. The recovery from a single intratracheal administration of zymosan A (2.5 mg/kg body weight) was monitored over 7 days. PMN and CL showed significant recovery from the day 1 level by 3 days post-exposure. Breathing frequencies and nitric oxide production showed significant recovery from the day 1 level by 4 days post-exposure. A good correlation (r^2 = 0.8) between PMN in BAL, CL, or nitric oxide production and the days post-exposure was observed.

936 MODIFIED ENDOTOXIN RESPONSE IN RATS PRE-TREATED WITH 1→ 3-β-GLUCAN (ZYMOSAN A).

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1→3-β-Glucans, derived from fungal cell walls, and endotoxin (LPS), derived from gram negative bacteria, are commonly found in organic dust. Both have been implicated in organic dust toxic syndrome. 1→3-β-Glucans belong to a class of compound called Biological Response Modifiers. In a previous study, we demonstrated that intratracheal instillation (IT) of 1→3-β-glucans (zymosan A) caused a dose-dependent inflammatory response in rats. The present study investigates whether 1→3-β-glucans modifies the pulmonary response of rats to endotoxin. Three experimental groups were investigated to evaluate the interaction of 1→3-β-glucans and endotoxin: Group A, IT-zymosan at day 1 and IT-LPS at day 2; Group B, IT-LPS at day 1 and IT-zymosan at day 2; Group C, IT zymosan and LPS at day 1, IT PBS at day 2. One day after these exposures, the following pulmonary response were monitored: (1) breathing frequency, (2) differential cell counts of bronchoalveolar lavage (BAL) cells, (3) chemiluminescence (CL) and (4) NO-dependent CL as a measure of alveolar macrophage activation, (5) nitric oxide production from alveolar macrophages, and (6) albumin and (7) lactate dehydrogenase (LDH) levels in the first acellular lavage fluid. Interaction between zymosan and endotoxin exposures was determined by the derivation from the sum of the individual effects of these agents. The results show that in group A (zymosan at day 1 before endotoxin at day 2) zymosan pretreatment decreased the subsequent pulmonary response to endotoxin. The other groups showed no significant difference between the results of combined exposure and the sum of the effects of endotoxin or zymosan exposure alone. These data suggest that the inhibitory effect of 1→3-β-glucans on pulmonary responsiveness to endotoxin exposure is apparent only when rats were pre-treated with 1→3-β-glucan.

937 β-1,3-GLUCAN TOXICITY ON HUMAN MONOCYTIC U937 CELLS.

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β-1,3-D-Glucan is a glucose polymer from yeasts/fungi and a known immunomodulator. It has anti-infection and antitumor effects and binds to CR3 (CD11b/18) on mononuclear phagocytes, neutrophils and NK cells. However, recently adjuvant effects of β-1,3-glucan on allergen responses have been reported. Moreover, acute exposure to β-1,3-glucan areosols is shown to induce symptoms of airways inflammation in healthy individuals. Since alveolar macrophages are main inflammatory responders in the airways, we examined whether β-glucan [1-200 μg/ml] was toxic to monocytes and induced synthesis of the proinflammatory cytokine IL-8. Un- or INFγ-differentiated human monocytic U937 cells were incubated with serum-treated or untreated particulate β-1,3-D-glucan MacroGard® (pMG). Cellular proliferation and survival were studied by incorporation of [3H]thymidine and exclusion of propidium iodide staining (flow cytometry), respectively. IL-8 secretion into the supernatants was examined by ELISA. Serum-treated pMG inhibited U937 proliferation concentration-dependently. The effect was abrogated by addition of a MoAb to CD11b. Survival of undifferentiated cells was strongly inhibited by untreated pMG, whereas similar inhibition of differentiated cells was only observed with serum-treated pMG, but not affected by anti-CD11b MoAb. In contrast to undifferentiated cells, serum-treated pMG induced IL-8 synthesis concentration-dependently in differentiated cells. The effect was reduced by anti-CD11b MoAb. The results indicate that β-glucan may be toxic to monocytic cells and promote synthesis of IL-8. The effects occur mostly after serum-opsonization of β-glucan and probably are mediated *via* CR3 (CD11b/18). This agrees with known enhanced effects on monocytes of β-glucan opsonized with iC3b. In vivo, inhaled β-glucan may activate complement in alveolar fluid, bind iC3b and be taken up *via* CR3 in alveolar macrophages. A toxic effect on these cells together with induced secretion of IL-8 may contribute to the reported airways inflammation after β-glucan exposure.

938 PERINATAL EXPOSURE TO ENVIRONMENTAL TOBACCO SMOKE (ETS) INDUCES BRAIN-DERIVED NEUROTROPHIC FACTOR (BDNF) AND TH2 CYTOKINES IN YOUNG RHESUS MONKEYS.

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Epidemiological studies have associated ETS exposure with asthma in early childhood. The role of Th2 cytokines in the allergic response has been well documented. Recent work suggests that neurotrophins are critical mediators between allergic inflammation and airway hyperresponsiveness. To examine the effects of ETS exposure during the perinatal period on cytokine response and neurotrophin levels in young rhesus monkeys, exposure was begun at 50 days gestational age at a total suspended particulate concentration of 1 mg per cubic meter, 6 hours per day, 5 days per week, and continued to 2.5 months postnatal age. Bronchoalveolar lavage (BAL) and measurement of interleukin (IL)-2, interferon-gamma, IL-4, IL-5, BDNF, and nerve growth factor (NGF) were done. Compared with control animals, significant increases were found in the differential percentages of monocytes, lymphocytes, and eosinophils in BAL recovered cells (287%, 347%, 478% of control, $p<0.05$, respectively), total protein level in the BAL fluid (228% of control, $p<0.05$), levels of IL-4 and BDNF in the cell culture supernatant of peripheral blood mononuclear cells (PBMCs) (170% and 440% of control, $p<0.05$, respectively), plasma level of BDNF (335% of control, $p<0.01$), and the IL-5 level in lung tissue extract (159% of control, $p<0.05$). Significant decreases in the levels of IL-2 in PBMC culture supernatant (81% of control, $p<0.05$) and NGF in BAL fluid (24% of control, $p<0.01$) were also detected. We conclude that exposure to ETS during gestational and postnatal periods of life causes chronic pulmonary inflammation and induces BDNF and Th2 cytokines in young rhesus monkeys.

939 PERINATAL EXPOSURE TO ENVIRONMENTAL TOBACCO SMOKE (ETS) INDUCES REGIO-SELECTIVE CYTOCHROME P450 AND OXIDATIVE STRESS IN THE LUNGS OF NEONATAL MONKEYS.

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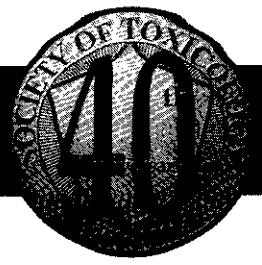
Exposure to ETS in children is known to be associated with increased adverse health effects including asthma and respiratory illness. However, the mechanisms by which ETS causes these effects are uncertain. The purpose of this study was to



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Preface

This issue of *The Toxicologist* is devoted to the abstracts of the presentations for the symposium, platform, poster discussion, workshop, roundtable, and poster sessions of the 40th Annual Meeting of the Society of Toxicology, held at the Moscone Convention Center, San Francisco, California, March 25–29, 2001.

An alphabetical Author Index, cross referencing the corresponding abstract number(s), begins on page 451.

The issue also contains a Keyword Index (by subject or chemical) of all the presentations, beginning on page 479.

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