1399 RAT CARDIOVASCULAR DYSFUNCTION PRIOR TO DEATH DURING EXPOSURE TO CONCENTRATED AMBIENT AIR PARTICLES.

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Groups of 12 rats with or without monocrotaline treatment (MT)-induced pulmonary inflammation were exposed by inhalation to either filtered air (FA) or concentrated urban air particles (CAPs) for five hours per day on three consecutive days. Continuous electrocardiograms (EKGs) were recorded on three members of each group during exposures. CAPs concentrations were approximately 200, 600, and 150 μ g/m^3, respectively, on day 1, 2, and 3 of exposure. During the exposure period, one MT, FA-exposed (8.3 %) and three MT, CAPs-exposed (25%) animals expired. Continuous EKG was recorded on one of the MT rats which succumbed on the third day of CAPs exposure. Death occurred 90 minutes (min) into exposure and was preceded by an initially steady heart rate (HR) for 15 min followed by a linear reduction in HR from 340 to 290 beats per min over the next 60 min. Concomitant increases in PR interval, QRS duration, HR standard deviation, low frequency HR variability power, and low-to-high frequency ratio were observed. QT interval contemporaneously decreased accompanied by a decrease in T wave height, deepening of the S wave, and emergence of possible U waves. Numerous premature ventricular contractions and other dysrhythmias were noted prior to demise. To our knowledge, this is the first continuous recording of cardiac death apparently induced by inhalation of CAPs. A similar mode of death (bradycardia and dysrhythmia followed by asystole) was reported in MT animals instilled with residual oil fly-ash particles (Watkinson et al, *Tox Sci* 41:209). Canines exposed to CAPs in our laboratory have also exhibited HR slowing. Furthermore, analysis of human data obtained from implantable cardiac defibrillators has associated bradycardic events with $PM_{2.5}$ elevation. Cardiac conduction system dysfunction may be an important mechanism of death associated with fine particle exposure in the MT rat. (Supported By: ES00002, ES08129, HL05947, and HL54958.)

1400 ACUTE CARDIORESPIRATORY EFFECTS OF PYRIDOSTIGMINE BROMIDE AND N,N-DIETHYL-m-TOLUAMIDE (DEET) IN RATS.

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Acute co-administration of a reversible, peripherally acting cholinesterase inhibitor, pyridostigmine bromide (PB), and a personal insect repellent, N,N-diethyl-m-toluamide (DEET), resulted in potentiation of letbality. This study was designed to explore the mechanism(s) of that lethal interaction. Whole body plethysmography was used to measure respiratory activity in conscious freely-moving rats, while cardiovascular function was monitored simultaneously through an arterial catheter, following acute i.p. administration of PB (2 mg/kg) and/or DEET (300 or 500 mg/kg). PB (2 mg/kg) alone stimulated respiration and increased blood pressure. Arterial pH levels were decreased, while pO_2 and pCO_2 remained at control levels. Administration of DEET (300 mg/kg) alone increased tidal volume and reduced blood pressure. Blood gases and pH levels were unaltered. A higher dose of DEET (500 mg/kg) also decreased respiratory and heart rate. Co-administration of PB (2 mg/kg) and DEET (300 mg/kg) increased tidal volume, decreased arterial pH, and elevated pCO_2. Heart rate and blood pressure declined progressively after drug co-administration. Pretreatment with atropine methyl nitrate reduced the individual effects of PB or DEET, and significantly increased survival after co-exposure to both agents. While changes in respiratory function contributed to the lethal interaction, it was concluded that the primary cause of death was circulatory failure. The results are consistent with a hypothesis that DEET depresses central cardiorespiratory control mechanisms and sympathetic outflow. In addition, PB-induced accumulation of acetylcholine at peripheral cholinergic receptor sites resulted in bradycardia that is postulated to further reduce cardiac output, causing progressive circulatory shock. Pretreatment with atropine methyl nitrate protected against circulatory collapse by preventing PB-induced bradycardia.

1401 ACCELERATION OF ATHEROSCLEROTIC PLAQUE FORMATION IN Apo E$^{-/-}$ MICE BY EXPOSURE TO TOBACCO SMOKE.

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Epidemiological studies have implicated active and passive smoking with increased risk of cardiovascular diseases. The present study was performed to determine if exposure to sidestream cigarrette smoke (SSCS) influences the development of experimental atherosclerotic plaque formation in a rodent model. Female Apo E$^{-/-}$ mice (n=20), maintained on a high fat diet, were divided into two equal groups. One group was exposed to SSCS in a whole-body exposure chamber set at a particulate concentration of 22±5mg/m^3 for a total of 6 hrs each day, 5 days a week. The second group was exposed to filtered ambient air and served as control. Elevated levels of blood carboxyhemoglobin and pulmonary CYP 1A1 were used to ascertain effective exposure of animals to smoke. The animals were killed after 3 months of exposure and their serum and aorta were collected for analyses. Both groups exhibited high serum cholesterol and triglyceride concentrations but no differences between the control and smoke-exposed groups were noticed. Image analysis of entire intimal area of the aorta covered by grossly discernable lesions demonstrated a significant increase in the smoke-exposed group. In agreement with these data there were significant increases in the aortic content of free and esterified cholesterol following smoke exposure. These results clearly demonstrate an enhancing effect of tobacco smoke exposure on the development of lesions in an atherosclerosis susceptible mouse model. (Supported by KTRB 5-41110 and the Gill Heart Institute.)

1402 ALLYLAMINE AFFECTS GLUCOSE UPTAKE IN RAT VASCULAR SMOOTH MUSCLE CELLS.

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A streptozotocin diabetic rat model was used to investigate the effects of allylamine-induced atherosclerosis. Vascular smooth muscle cells (VSMC) from allylamine treated diabetic and non-diabetic rats were used to investigate deoxyglucose uptake as an insulin-sensitive response. VSMC from untreated animals exhibited a 1.8-fold increase over basal uptake. The observed effect appears to be mediated by specific glucose transporters as evidenced by inhibition of the effect in the presence of high glucose. Allylamine treatment inhibits both basal and insulin-stimulated uptake. In the absence of insulin approximately 33% inhibition was observed. This inhibition did not change significantly in the presence of insulin suggesting an alteration of insulin-sensitive response. However, cells remained sensitive to insulin effects following *in vitro* exposure of non-treated cells to 5μM allylamine during the course of the uptake. In VSMC from non-allylamine treated diabetic rats , basal and insulin-stimulated uptake were decreased by about 38% and 30%, respectively. Allylamine treatment does not decrease basal or insulin-stimulated uptake beyond the decrease attributed to the diabetic state. However, allylamine appears to exert an effect on glucose uptake in non-diabetic animals that is not insulin dependent. (Supported by NIH/NCRR RCMI Grant No. G12RR03045-11.)

1403 COLLAGEN AND ELASTIN DEPOSITION BY VASCULAR SMOOTH MUSCLE CELLS IN RESPONSE TO INHIBITION OF SEMICARBAZIDE-SENSITIVE AMINE OXIDASE.

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Aortic vascular smooth muscle cells (VSMC) have the highest tissue-specific activity of Semicarbazide-Sensitive Amine Oxidase (SSAO) - an amine oxidase who's physiological function is undefined. This cell type is also responsible for production of collagen and elastin within the mammalian aorta. Our laboratory has demonstrated that *in vivo* SSAO inhibition results in vasculotoxicity in developing rats exemplified by lesions of the medial elastin architecture. This study examines changes in collagen and elastin deposition by cultured rat VSMC exposed to natural and synthetic SSAO inhibitors. Collagen and elastin fractions were isolated from Rat VSMC cultures treated for 30 days with SSAO inhibitors. Semicarbazide (1x10^{-6} M), benzylamine (1x10^{-5} M), and (*E*)-2-phenyl-3-chloroallylamine (Marion Merrell Dow; 5x10^{-6} M) - which are relatively specific inhibitors of SSAO - substantially reduced the amount of mature elastin deposited by VSMC while only slightly affecting collagen deposition. $ -aminopropionitrile (8x10^{-3} M) - an inhibitor of lysyl oxidase - predictably reduced insoluble col-

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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 38th Annual Meeting of the Society of Toxicology, held at the Ernest N. Morial Convention Center, New Orleans, Louisiana, March 14-18, 1999.

An alphabetical Author Index, cross referencing the corresponding abstract number(s), begins on page 419.

The issue also contains a Keyword Index (by subject or chemical) of all the presentations, beginning on page 444.

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