1723 ENDOTHELIAL STRUCTURAL INTEGRITY IS MAINTAINED DURING ENDOTOXIC SHOCK IN A TYPE-1 INTERLEUKIN-1 RECEPTOR KNOCKOUT MOUSE

E T Sutton[1,2], J G Norman[3], M Glaccum[4], I S Richards[2]. *Departments of Physiology and Biophysics and Surgery[3], College of Medicine and Department of Environmental and Occupational Health[2], College of Public Health, University of South Florida, Tampa, FL, Immunex Corporation, Seattle, WA[4]*

The derangement of arterial endothelial cell morphology is a good indicator of a severe shock state. Since interleukin-1 (IL-1) has been implicated in this process, we examined the structural integrity of aortic endothelial cells during endotoxemia in animals genetically devoid of the type 1 IL-1 receptor. Endotoxin (10 mg/kg *Escherichia coli* injected intraperitoneally) (LD_{100}) or saline vehicle was administered to adult male C57BL/129J wild-type control mice and C57BL/129J knockout mice possessing a homozygous deletion of the type-1 IL-1 receptor. The integrity of the aortic endothelium was determined by comparisons of ultrastructure. Mice injected with sterile vehicle showed normal endothelial ultrastructure with intact membranes. Wild type and knockout control animals receiving saline vehicle showed complete maintenance of aortic endothelium (29.11 ± 0.27 and 30.85 ± 0.21 intact endothelial cells/mm of internal elastic lamina (IEL), respectively, p = N.S.) Endotoxin treated wild type animals showed extensive endothelial damage with most sections showing only denuded internal elastic lamina on the luminal surface (1.83 ± 0.38 cells/mm IEL, $p<0.001$ vs control). Knockout animals treated with endotoxin showed complete maintenance of endothelial structural integrity (34.08 ± 0.57 cells/mm IEL, $p<0.001$ vs endotoxin treated wild type) with ultrastructural morphology appearing identical to those given saline vehicle. The maintenance of endothelial integrity in animals devoid of the IL-1 receptor confirms earlier observations of endothelial cell protection with IL-1 receptor antagonism and suggests that IL-1 contributes significantly to sepsis-induced endothelial damage.

1724 ANTIMONY INDUCTION OF HEAT SHOCK PROTEINS IN NEONATAL RAT CARDIAC MYOCYTES

M Tirmenstein, J Snawder, P Mathias. *National Institute for Occupational Safety and Health, Cincinnati, OH*

Antimony is a hard, brittle metal that has extensive uses in industry. Antimony-containing compounds are used in the manufacture of paints, ceramics, pyrotechnics, fire retardants and glass. The National Institute for Occupational Safety and Health estimates that more than 250,000 individuals in the United States are exposed to antimony compounds at work. Antimony-containing compounds produce cardiac functional alterations and toxicity in both experimental animals and humans. Previously, we reported that potassium antimonyl tartrate (PAT) induced oxidative stress and was directly toxic to cultured neonatal rat cardiac myocytes. Little is known, however, regarding the biochemical effects of nonlethal concentrations of PAT on cardiac myocytes. Numerous studies have reported the induction of stress or heat shock proteins in a wide variety of cellular systems following exposure to metals. Heat-shock proteins are a ubiquitous group of proteins that are synthesized in response to heat and other environmental stress and are thought to afford protection against cell toxicity. The stress protein heme oxygenase is especially susceptible to induction by metals. Drummond and Kappas demonstrated that PAT as well as other antimony-containing compounds were potent inducers of heme oxygenase in the liver and kidney of rats, but the effects of PAT on the heart were not examined. In the present study, sublethal concentrations of PAT were examined in neonatal rat cardiac myocytes for PAT-induced changes in cellular glutathione levels, heme oxygenase and stress protein expression. Our results indicate that an 18 hr exposure to low concentrations of PAT (5–25 μM) increases cellular glutathione levels, heat shock protein 70 and heme oxygenase activity in cardiac myocytes in a concentration-dependent manner.

1725 SULFUR MUSTARD INDUCTION OF DERMAL MICROBLISTERS IN A WEANLING PIG MODEL

T. H. Snider, J. A. Blank, F. R. Reid, C. T. Olson, and D. W. Hobson. *Battelle Memorial Institute. Columbus, OH*

Sulfur mustard (SM; 2,2'-dichloroethyl sulfide) can produce incapacitating blisters in humans following dermal exposure. The hairless guinea pig (HGP) is one of the few animal models which has been shown to exibit microscopic epidermal-dermal separation (microblisters) following SM exposure. Because the HGP is in short supply, studies were conducted to confirm that weanling pigs exhibit microblisters and to evaluate the utility of the pig as an alternative model for studying the blistering process. Weanling pigs were percutaneously exposed for varying lengths of time to SM. One day following exposure, skin light reflectance measurements were taken to assess erythema. The animals were sacrificed and skin specimens were taken, processed, and stained for histopathological evaluation. Results from these studies demonstrate that the weanling pig skin exhibits erythema and pathologic changes similar to those reported in SM-exposed HGP skin. These data indicate that the weanling pig could be used as an alternative model to the HGP for studying microblister. [Supported by USAMRDC Contract DAMD17-89-C-9050]

1726 SUBCHRONIC TOXICITY ASSESSMENT OF LY315535, A 5-HT AGONIST/MUSCARINIC ANTAGONIST IN BEAGLE DOGS

B M Palate, B O Depelchin, M M Masson. *Lilly Development Centre, Mont-Saint-Guilbert, Belgium.* Sponsor: G F Rush

Daily oral doses (0.8, 2 or 5 mg/kg) of LY315535, a potent 5-HT1a agonist with mild muscarinic antagonist activities, were administered to beagle dogs for 1 month. At 5 mg/kg, clinical signs were restricted to tremors, increased muscular tone and hypersalivation. Occasional convulsions, reduced activity and abnormal gait were also observed; These clinical signs were minimal at 2 mg/kg. Tolerance to central nervous system effects did not develop. The drug-related clinical signs were of limited duration and were likely to be the result of the pharmacological mechanism of action of LY315535. Transient decreases in body weight gain were observed in animals receiving 2 or 5 mg/kg and increases in respiratory rates were observed in animals given 5 mg/kg (5-fold), and 2 mg/kg (2-to 3-fold). Heart rate was significantly increased in dogs given 5 mg/kg. In a single female from this group (5 mg/kg), sinus tachycardia, increased PQ duration, increased alanine aminotransferase (2-fold), aspartate aminotransferase (7-fold) and creatine phosphokinase (27-fold) activities were noted. Except for these findings, the only notable change in clinical chemistry was an increase in cholesterol values in dogs given 5 mg/kg. No changes in serum gastrin levels and morphometry of the stomach wall were detected. Medial hemorrhagic necrosis was observed in the small arteries of the heart, gastrointestinal tract, kidney and thymus of a single high-dose male dog. This type of arterial lesion has been reported with vasoactive drugs (Van Vleet *et al.*, 1991). The lesions observed in this study may be due to the action of LY315535 on arterial smooth muscle 5-HT receptors (Mylecharane, 1990).

1727 ETHANOL POTENTIATES THE DEPRESSANT EFFECTS OF COCAINE IN HUMAN FETAL MYOCARDIUM IN VITRO

I S Richards. *Department of Environmental and Occupational Health, College of Public Health, University of South Florida, Tampa, FL*

Cocaine and ethanol use is wide spread in our society and is not uncommon in pregnant women. Previous work from this center demonstrated that acute exposure to moderate concentrations of cocaine or ethanol, singly, produced significant effects on fetal myocardial action potentials and contractility *in vitro* and may provide a mechanism to account for fetal arrhythmias or sudden death *in utero*. The use of fetal tissue in this *in vitro* study was approved by the University of South Florida's Institutional Review Board which governs policies and procedures for research involving human subjects. Fetal hearts (12-14 weeks) were obtained at the time by elective abortion and transported to the laboratory in cold physiological salt solution (PSS). In the laboratory, a small portion of the ventricular wall (~2 × 6 mm) was pinned, endothelial surface up, in a specially constructed Sylgard-coated 2ml plexiglass perfusion chamber. The force of muscle contractions and transmembrane potentials were measured simultaneously. Developed force was measured with a micro-force transducer, and transmembrane potentials using standard 3M KCl-filled glass microelectrodes. Preparations were stimulated at 2 Hz with supramaximal electrical pulses which were delivered across bipolar platinum electrodes. Throughout the course of an experiment fresh PSS was oxygenated and superfused through the tissue bath. The temperature in the bath was maintained at 37°C. When a concentration of cocaine that singly produced moderate myocardial depression (200ng/ml) was administered to fetal myocardium equilibrated with PSS containing ethanol at a final concentration of 0.02%, significant depression and or block of action potentials and contractility was observed. Ethanol (0.02%) singly did not produce any significant effects on the heart. This study suggests that the combined use of cocaine and ethanol may produce myocardial depression greater than that predicted from the effects of these chemicals when used individually.

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Preface

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The issue also contains a Keyword Index (by subject or chemical) of all the presentations, beginning on page 375.

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