atherosclerosis, hypertension and diabetes. The decline in NO bioavailability due to accelerated destruction by superoxide, is a common mechanism underyling endothelial dysfunction and may be relevant as PM is a facile generator of reactive oxygen species. While the precise locus of generation of radicals in response to PM is debated, there is reason to believe that the vasculature may be key to modulation of PM effects. Experiments in animal models and humans suggest that PM mediated effects on the vascular endothelial function are rapid and may occur within hours to days following exposure. Endothelial dysfunction mediated via PM may then play a critical role in setting the stage for vascular inflammation. Data from our laboratory suggest that acute and sub-acute exposure markedly alters endothelial function through NADPH oxidase dependent mechanisms altering the propensity to other insults such as high fat feeding and pressor agents. These findings have important implications for the synergistic effects of PM with other atherosclerotic risk factors.

1253 EFFECTS OF INHALED DIESEL EXHAUST ON VASCULAR OXIDATIVE STRESS AND ENOS FUNCTION.

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Environmental air pollution has been associated with increased hospital admissions and death due to heart failure. However, the exact mechanism(s) by which environmental air pollution affects the heart and vasculature is currently unknown. Heart failure and diabetic patients have pre-existing endothelial cell dysfunction and recent studies have found that exposure to environmental air pollution enhances vasoconstriction in these populations. Work in our laboratory has shown that diesel exhaust (DE), a major component of ambient urban air, could enhance vasoconstriction of mouse coronary arteries and, in a model of heart failure, increase thoracic venous pressure; these effects could be linked to enhanced vascular oxidant generation. Thus, we hypothesized that DE could enhance vasoconstriction in arteries and veins through uncoupling of endothelial nitric oxide synthase (eNOS). To test this hypothesis, we first exposed animals, whole body, to DE at 350μg/m^3 for 4h, after which mesenteric arteries and veins were isolated. Results from these experiments show that inhaled DE enhances the vasoconstrictive effects of ET-1 in veins more than arteries. L-NAME, an eNOS inhibitor, normalized the control vessels to the diesel exhaust vessels implicating an uncoupling of eNOS as a mechanism for enhanced vasoconstriction. These data suggest that exposure to inhaled DE may induce venous congestion in susceptible subjects through enhanced vasoconstriction due to vascular oxidative stress.

1254 REGULATION OF ENDOTHELIAL CELL ADHESION MOLECULES BY ACROLEIN, AN ENVIRONMENTAL ALDEHYDE.

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Acrolein, a toxic aldehyde generated during combustion of fossil fuels, is also generated endogenously during lipid peroxidation. Adhesion molecules ICAM-1 and VCAM-1 expressed on endothelial cells (EC) upon cytokine stimulation facilitate leukocyte adhesion and migration. In inflammatory diseases, the ectodomain cleavage of these adhesion molecules is augmented releasing soluble ICAM-1 (sICAM-1) and VCAM-1 (sVCAM-1) into the plasma. Mice exposed to acrolein (5 mg/kg by gavage) showed a significant (36 ±2%, P<0.001) reduction in the plasma levels of sICAM-1 at 4h after the exposure that persisted up to 24h (20±1%, P<0.001) when compared with water-fed controls. Human ECs were exposed to 0-10 μM acrolein for 1h in media without serum, allowed to recover for 24h, stimulated with TNF-α for 16h to induce adhesion molecule expression and cleavage, and then sICAM-1 and sVCAM-1 in the media were measured. A dose-dependent reduction in the levels of sICAM-1 (2-32%) and sVCAM-1 (17-63%) was observed. In such studies, TNF-α-induced JNK phosphorylation was diminished, but ERK 1/2 and p38 were unaffected by acrolein pretreatment. Monocyte adhesion to acrolein-exposed ECs was augmented (1.3-1.4 fold). However, acrolein did not affect basal sICAM-1 release in ECs virally-transfected with ICAM-1 (in the absence of cytokine). We have reported that ICAM-1 cleavage is mediated by the matrix metalloproteinase (MMP) sub-family, TNF-α converting enzyme (TACE) (J. Biol Chem. 2006; 281:3157). Expression of TACE mRNA (but not the levels of endogenous MMP inhibitors, TIMP-1, -2 and -3) and protein levels were marginally decreased in acrolein-exposed ECs. These results indicate that acrolein down regulates the shedding of ICAM-1 and VCAM-1 perhaps through JNK inhibition, and thus, augments leukocyte adhesion to EC.

1255 ULTRAFINE PARTICULATE MATTER INHALATION ATTENUATES MICROVASCULAR ENDOTHELIAL NITRIC OXIDE PRODUCTION.

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We have shown that pulmonary exposure to fine particulate matter (PM) impairs endothelium-dependent dilation in systemic arterioles. The purposes of this study were to: determine if PM size affects the severity of microvascular dysfunction, characterize alterations in endogenous nitric oxide (NO) production, and identify systemic mechanisms that may influence NO production after PM inhalation. Rats were exposed to fine or ultrafine TiO_2 via inhalation (primary particle sizes of ~1 μm, and ~21 nm, respectively) at depositions of 10-100 μg/rat. The spinotrapezius muscle was prepared for intravital microscopy 24 hrs after exposures. Intraluminal infusion of the Ca^{2+} ionophore A23187 was used to evaluate endothelium-dependent arteriolar dilation. Microvascular NO production was measured with a Clarke-Type electrochemical NO sensor. In control rats, A23187 infusion produced dose-dependent arteriolar dilations. In rats exposed to fine TiO_2, A23187 infusion elicited vasodilations that were blunted in proportion to pulmonary particle deposition. In rats exposed to ultrafine TiO_2, A23187 infusion produced arteriolar constrictions or significantly impaired vasodilator responses as compared to those observed in rats exposed to an identical pulmonary load of fine particles. Endogenous microvascular NO production was attenuated after ultrafine TiO_2 inhalation in a dose-dependent manner. Treatment with either 4-aminobenzoic hydrazide or apocynin partially restored NO production and normal microvascular function. These results are consistent with the hypothesis that systemic inflammatory mechanisms are active after PM exposure and such mechanisms disturb normal microvascular function.

1256 DIESEL EXHAUST EXPOSURE INCREASES BLOOD PRESSURE, SYMPATHETIC ACTIVITY, AND CORONARY ARTERY CONSTRICTOR FUNCTION.

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Some individuals experience acute cardiovascular events following exposure to air pollutants that may be triggered by vasospasm. Because the pollutant diesel exhaust (DE) has been shown to increase endothelin (ET) synthesis and sympathetic nervous system activity (SNSA), these events may be key to such adverse cardiovascular sequelae. If DE also augments coronary artery constriction to ET-1, this would exacerbate cardiac insufficiency following exposure to DE. We hypothesized that acute exposure to moderate levels of DE augments ET constrictor sensitivity and diminishes endothelium-dependent dilation. Rats were exposed to 5 hrs of DE (300 μg/m^3) or Filtered Air (FA). Arterial pressure (AP), electrocardiograms (ECG) and heart rate (HR) were recorded using telemetry. Coronary arteries were obtained after DE exposure to measure ET-1 constrictor responses and agonist-induced dilator responses. HR variability was derived from ECG (ratio of low to high frequency of transformed RR interval) and used as an index of SNSA. Tissue from the heart, intraseptal coronary artery, lung and aorta were collected immediately after DE exposure to determine ET-1/3 and $ET_{A/B}$ receptor mRNA using real time PCR. AP was elevated in rats exposed to DE compared to air exposed rats ($p<0.05$). SNSA was also greater in DE rats compared to controls. In isolated coronary arteries (inner diameter = 180 ± 11 μm) from FA and DE rats, DE augmented ET-1 constrictor responses and diminished acetylcholine-induced vasodilation compared to arteries from FA-exposed rats ($p<0.05$). Acute DE exposure did not alter ET peptide or receptor mRNA suggesting the increased constriction to ET-1 is caused by altered signal transduction rather than changes in receptor expression. In summary, DE exposure may increase cardiac work load concurrent with decreased efficiency of oxygen delivery. These combined changes may contribute to the detrimental cardiac effects of DE and the increased incidence of cardiac events observed following this exposure.

1257 ENDOTHELIAL DYSFUNCTION AND ENVIRONMENTAL ALDEHYDES: ACROSS SPECIES COMPARISONS.

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Reactive aldehydes are generated endogenously during lipid peroxidation and inflammation and are ubiquitous environmental pollutants. Protein adducts of acrolein and 4-hydroxy-trans-2-nonenal (4HNE) are increased in human atherosclerotic plaques, neuronal membranes of patients with Alzheimer's disease, and plasma of heart failure patients. To understand the potential vascular complications

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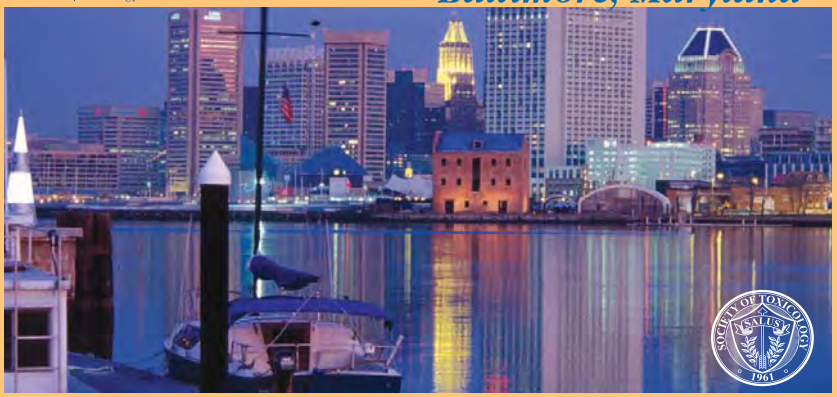

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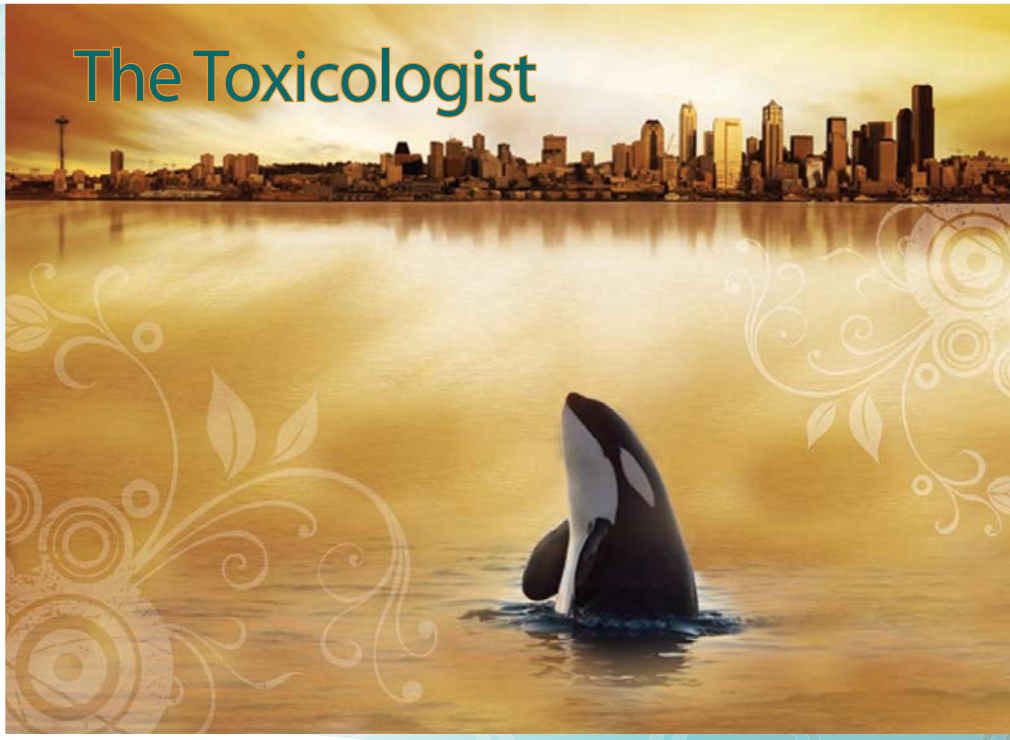

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