toward natural death, AKR/J mice showed enhanced permeability of a soluble tracer particle. These results suggest a potential mechanism for increased sensitivity of the aged to inhaled particulate matter.

707.8

Dietary Potassium Oxonate Increases Uric Acid in Rat Plasma and Bronchoalveolar Lavage Fluid

Brian Kain[1], Dale Porter[2], Ken P. Blemings[1], Hillar Klandorf[1]. [1]Animal & Vet. Science. West Virginia University, PO Box 6108, Morgantown, WV 26506, [2]National Institute for Occupational Safety and Health, Morgantown, WV

Uric acid (UA) may be an important antioxidant, but its role in the lung has not been investigated. It is our hypothesis that by raising UA concentrations, silica-induced pulmonary damage may be ameliorated. In the first of a two part study, 52 male Sprague-Dawley rats were randomized to four dietary treatments of 0, 2.5, 5.0, or 7.5% potassium oxonate (PO), an inhibitor of uricase. Four rats per group were sacrificed on days 10, 20, and 30. Plasma and bronchoalveolar lavage (BAL) fluid were analyzed for UA by HPLC. Dietary PO increased plasma ($p<0.05$), and BAL fluid ($p=0.06$) UA concentrations approximately four fold. PO had no effect on growth rate, BAL albumin, lactate dehydrogenase, alveolar macrophage and polymorphonuclear leukocyte cell yields, or NO-dependant AM chemiluminescence ($p>0.05$). The ability of dietary PO to increase UA levels, and its lack of non-specific toxicity, will be utilized in future studies designed to investigate the effect of increased UA levels on silica-induced pulmonary disease. This research is supported by NIOSH and WV Ag. & Forestry Exp. Station Project H-393.

CELL INJURY AND CELL DEATH/APOPTOSIS (708.1-708.12)

708.1

Light-induced retinal degeneration: DNA damage and repair

William C. Gordon, Walter J. Lukiw, Nicolas G. Bazan. Neuroscience Center, Louisiana State University Health Sciences Center, 2020 Gravier Street Suite D, New Orleans, LA 70112

Bright light causes photoreceptor loss. Early studies showed many TUNEL-positive (T+) photoreceptors after light treatment, but fewer than this died. Therefore, we compared DNA damage and cell loss. Rats were light treated; damage measured by TUNEL, laddering, and highly repetitive short interspersed nuclear element (SINE) analysis at 6 hr intervals; T+ cells counted per retina on a top to bottom meridian; and cell loss determined at 10d. TUNEL, ladder, and SINE analysis at 6 hr intervals each showed 2 DNA damage peaks 24 hr apart, but T+ cell numbers for both peaks exceeded those lost at10d. 2 DNA damage waves could result from: 1 set of damaged cells, repairing until the mechanism is damaged, then continuing toward death; 2 different cell sets showing DNA damage 24 hr apart. Case 1: DNA damage occurs but is masked at midpoint by a brief repair mechanism. Case 2: 2 damage waves occur, a repair mechanism corrects the first cell set but not the second. Number of cells lost at 10d is less than all T+ cells. Both cases imply an active photoreceptor DNA repair process, suggesting that maintenance of this in-house mechanism may provide an alternative approach for rescue of neurons with stress-induced damage. (EY05121)

708.2

Bcl-w MEDIATES NEUROPROTECTION IN ALZHEIMER DISEASE

Xiongwei Zhu[1], Yang Wang[2], Osamu Ogawa[1], Hyoung-gon Lee[1], Arun K Raina[1], Hisashi Fujioka[1], Heather Boux[3], Shun Shimohama[4], Craig S Atwood[1], George Perry[1], Mark A Smith[1]. [1]Institute of Pathology, Case Western Reserve Univeristy, 2085 Adelbert Road, Cleveland, OH 44106, [2]Department of Biochemistry, Case Western Reserve Univeristy, Cleveland, OH, [3]StressGen Biotechnologies Corporation, Victoria, British Columbia Canada, [4]Department of Neurology, Kyoto Univeristy, Kyoto, Japan

AD is characterized by widespread neuronal cell loss. The causes and mechanisms underlying such neuronal death are controversial and none more so than whether apoptosis plays a role. Although neurons in AD face a wide assortment of apoptogenic stimuli, the temporal dichotomy between the acuteness of apoptosis vs. the chronicity of AD suggests that apoptotic events should be very rare in AD. Therefore, we speculated that survival factor(s) must be involved in preventing the apoptotic process. In this study, we investigated Bcl-w, a novel pro-survival member of the Bcl-2 family. Bcl-w, although constitutively expressed at low levels in brains of control cases, was found to be overexpressed in brains of AD cases by both IHC and immunoblot. Upregulated Bcl-w was detected predominantly in neurons and ultrastructurally localized to PHF. Given that neuronal death in AD is believed to be triggered by an increased production of Aβ, it was interesting to find that exposure of M17 neuroblastoma cells and primary neuronal cultures to subtoxic conc. of Aβ upregulated Bcl-w protein, which may be a protective response. To pursue this further, we stably overexpressed Bcl-w in M17 cells. Cells overexpressing Bcl-w were significantly protected from both staurosporine-induced apoptosis and Aβ-induced neurotoxicity compared to vector-transfected controls. Taken together, these in vitro and in vivo data suggest that Bcl-w plays a neuroprotective role in neurons in AD brain.

708.3

Allicin-induced, apoptosis and caspase-independent cell death pathway in human gastric epithelial cells

Yong-wha Lee, Sook-young Park, Eun-wha Son, Kyung-Ran Kim, Dong-Kyun Ryu, Dong-Kwon Rhee, Suhkneung Pyo. Sungkyunkwan University, Jangan-gu chunchun-dong 300, Suwon, Kyunggi-do 440746 Korea, Republic of

Garlic (Allium sativum) has been used as a general food and a remedy in Oriental for a long time. Garlic compounds have been also shown to inhibit growth of tumors and to modulate the activity of carcinogenesis. Since allicin (dially sulfide) is one of the active principles in garlic, the effects of allicin on growth and survival in human gastric epithelial cells were evaluated in terms of cell viability, nuclear morphology, cell cycle analysis, DNA fragmentation, caspase activity, and poly (ADP ribose) polymerase (PARP) cleavage. Allicin treatment inhibited cell growth and resulted in typical apoptotic nuclear change in a dose dependent manner. In addition, cell cycle analysis revealed subdiploid cells suggesting apoptosis, which was confirmed by demonstration of DNA fragmentation. However, pan-caspase inhibitor could not prevent allicin-induced apoptosis. Futher, allicin treatment did not lead to cleavage of caspase-3, caspase-8, or PARP, indicating that allicin-induced apoptosis was independent of caspases. Moreover, apoptotic bodies formation and DNA cleavage by allicin were not prevented by caspase inhibitor. Taken together, these results demonstrate that allicin induced apoptosis in human gastric epithelial cells and this form of cell death is caspase independent.

708.4

Caspase Activity is Increased in Platelets From Type 2 Diabetic Rats

Zoe Cohen, Grace F Davis-Gorman, Paul F McDonagh. Surgery, University of Arizona, 1501 N. Campbell Ave. P.O. Box 245071, Tucson, Arizona 85724

Type 2 diabetes, the most prevalent form of diabetes, is associated with a hypercoagulable condition that may be due to activation of platelets. The mechanisms governing increased platelet activation in type 2 diabetes are unclear. Interestingly, the changes that activated platelets undergo mirror those observed in apoptosis. However, it is not clear if the same proteases involved in apoptosis are involved in platelet activation. Therefore, the aim of this study was to examine whether caspases, known to be involved in apoptosis, are activated in the platelets of type 2 diabetic rats. Platelets were isolated from blood of Sprague-Dawley rats, lean control rats, and type 2 diabetic rats (ZDF, Charles River Genetic Models). Caspase 2,3,6,8, and 9 activity were quantified using a colorimetric assay. We found that caspase 3,6 and 8 activity were significantly increased in the diabetics as compared to controls ($p\leq0.05$). Caspase activity may be involved in chronic activation of the platelets resulting in a hypercoagulable state. Supported by NIH 58859 and NIH HLB 07429.

708.5

CTLA-4·Fas Ligand functions as a *trans* signal converter protein in bridging antigen presenting cells and T cells

Jui-Han Huang, William R. Schmidt, Mark L. Tykocinski. Pathology and Laboratory Medicine, University of Pennsylvania, 422 Curie Blvd, Philadelphia, PA 19104

Costimulator blockade and *trans* inhibitory signaling, using agents such as CTLA-4·Ig and Fas ligand (FasL), respectively, have been invoked as alternative strategies for suppressing pathogenic T cells. This study describes a novel hetero-bifunctional fusion protein, CTLA-4·FasL, designed to combine within a single protein both costimulator blocking and trans inhibitory signaling potentials. A CTLA-4·FasL fusion protein bound to either $B7^+$ Daudi cells or Fas^+ Jurkat cells as shown by immunofluorescence and flow cytometry. CTLA-4·FasL induced apoptosis of Jurkat cells and apoptosis was markedly enhanced by the addition of

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