is accompanied by increased insulin, insulin-like growth factor I, and oxidative stress which are mechanistically linked to carcinogenesis, and increased tumor necrosis factor in obese animals. In rats maintained on a high fat diet, obesity potentiates liver necrosis induced by acetaminophen, furosemide, and allyl alcohol. Obesity increases kidney necrosis induced by acetaminophen and furosemide. Aminoglycoside antibotics are also significantly more nephrotoxic in obese human patients and overfed rats. In all of these cases, toxicity increases despite dosing normalization to fat-free mass. This argues that pharmacodynamic factors are responsible. Obesity induces CYP2E1 activity in rat liver and kidney, which may contribute to increased necrosis caused by these xenobiotics requiring metabolic activation. The obese rat kidney shows increased rates of gentamicin uptake, which may contribute to increased renal cell death. Thus, metabolic and other changes in obesity may lead to an environment that broadly favors increased sensitivity to chemical-induced toxicity. This may contribute to higher incidences of liver and kidney disease in the obese population.

1505 OBESITY, METABOLIC SYNDROME X AND INFLAMMATION

P. Dandona. *SUNY-Buffalo, Buffalo, NY.* Sponsor: C. Corton.

Insulin resistance syndrome (IRS), also known as metabolic syndrome, is now well recognized as a distinct pathological and clinical entity, with multiple significant ramifications for both the high-risk individual as well as the public health system. The primary contributory cause is obesity. Common manifestations associated with IRS may include atherosclerotic heart disease, hypertension, impaired glucose tolerance, dyslipidemia, polycystic ovary syndrome, and hypercoagulability. Infection and inflammation are commonly associated with insulin resistance, and visceral obesity is associated with a chronic, low-grade inflammatory state, suggesting that inflammation may be a potential mechanism whereby obesity leads to insulin resistance. Moreover, adipose tissue is now recognized as an immune organ that secretes numerous immunomodulatory factors and seems to be a significant source of inflammatory signals known to cause insulin resistance. Therefore, inflammation within white adipose tissue may be a crucial step contributing to the emergence of many of the pathologic features that characterize the metabolic syndrome and result in diabetes and atherosclerosis. This talk describes the molecular basis of IRS and the role of proinflammatory cytokines and hormones released by adipose tissue in generating the chronic inflammatory profile associated with visceral obesity.

1506 DIET-INDUCED DIABETES AS A MODULATOR OF CHEMICAL TOXICITY IN THE LIVER

H. Mehendale. *Department of Toxicology, University of Louisiana, Monroe, LA.*

Obesity is a predisposing factor for diabetes. Diabetes is a complex disease that leads to physiological and molecular changes in the liver. In a type 2 diabetes rat model that closely resembles diabetic patients, usually nonlethal doses of hepatotoxicants such as allyl alcohol, CCl4 or thioacetamide cause 80 to 100% mortality. Even though liver injury initiated by CCl4 and thioacetamide is the same in non-diabetic and diabetic rats, it progresses only in the latter, ending in hepatic failure, and death. Hepatomicrosomal CYP2E1, lipid peroxidation, glutathione, and covalent binding of CCl4 and thioacetamide to liver tissue were the same in both groups, suggesting that bioactivation-based liver injury is not higher in diabetic rats. Stimulation of compensatory S-phase DNA synthesis and cell division in the liver were inhibited in the diabetic rats. In contrast, in the non-diabetic rats robust tissue repair resulted in regression of injury and survival after toxicant exposure. To investigate the reason for inhibition of S-phase DNA synthesis in diabetic rats after toxicant challenge, MAPK pathway was investigated (0 to 24 h) after CCl4 challenge. Activation of ERK 1/2 was down regulated while p38 was activated within 3 h in the diabetic rats after CCl4 administration. Cyclin D1 and cyclin dependent kinase (cdk) 4/6 expression were lower in the diabetic rats compared to the non-diabetic rats after CCl4 administration, resulting in decreased phosphorylation of retinoblastoma protein (p-pRB). Thioacetamide administration also resulted in down regulation of cyclin D1 expression and p-pRB in the diabetic rats. Thus, down regulation of mitogenic signaling in the diabetic rats leads to problems at the G0/G1 to S-phase, impeding cell division needed for of tissue repair, thereby explaining the progression of liver injury after exposure to hepatotoxicants. In conclusion, type 2 diabetes increases sensitivity to structurally and mechanistically dissimilar hepatotoxicants (CCl4 and thioacetamide) due to accelerated expansion of liver injury as a consequence of impaired compensatory tissue repair.

1507 OBESITY AND INCREASED SUSCEPTIBILITY TO CHEMICALLY-INDUCED NEURODEGENERATION

J. O'Callaghan. *CDC-NIOSH, Morgantown, WV.*

Obesity is a major risk factor associated with a variety of human disorders. While its involvement in disorders such as diabetes, coronary heart disease and cancer have been well characterized, it remains to be determined if obesity has a detrimental effect on the nervous system. To address this issue we determined whether obesity serves as a risk factor for neurotoxicity. Model neurotoxicants, methamphetamine (METH), 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and kainic acid (KA), known to cause selective neurodegeneration of anatomically distinct areas of the brain, were evaluated using two models of obesity, leptin-deficient (ob/ob) mice and the diet-induced obesity (DIO) mouse model. Administration of METH or KA resulted in mortality among ob/ob mice but not among their lean littermates. Assessments of multiple indices neurotoxicity provide a consistent portrait: obese mice show enhanced neuronal damage and astrogliosis in comparison to their lean littermates. While METH and MPTP caused striatal dopaminergic nerve terminal degeneration (decreased striatal dopamine and tyrosine hydroxylase protein) and astrogliosis (increase in glial fibrillary acidic protein) in the lean mice, these effects were exacerbated in ob/ob mice. Similarly, exacerbation of neuronal injury after METH or MPTP was also observed in the DIO model of obesity. Consistent with the dopaminergic neurotoxicity seen in obese mice, KA caused extensive hippocampal neuronal degeneration, as determined by Fluoro-Jade B staining, decreased microtubule-associated protein 2 immunoreactivity and increased GFAP only in the ob/ob mice. The neurotoxic outcome in ob/ob mice remained exacerbated even when lean and ob/ob mice were dosed with METH or KA based only on a lean body mass. Administration of METH or KA also resulted in the upregulation of the mitochondrial uncoupling protein-2 to a greater extent in the ob/ob mice, an effect known to reduce ATP yield and facilitate oxidative stress and mitochondrial dysfunction. Thus, the obese condition may constitute a potential risk factor for susceptibility to neurotoxicity/neurodegeneration.

1508 DIET, OBESITY AND CHEMICAL CARCINOGENESIS: EXPERIMENTAL APPROACHES

S. Hursting. *NCI, Rockville, MD.* Sponsor: C. Corton.

Calorie restriction (CR) has been shown to increase resistance to chemically-induced cancers, while obesity increases susceptibility to many cancers. Animal models displaying specific genetic susceptibilities for cancer, such as mice deficient in the p53 or Apc tumor suppressor genes, are useful to determine the relationship between nutrition (particularly energy balance/obesity) and molecular carcinogenesis. We showed that in p53-/- mice CR increases the latency of spontaneous tumor development (mostly lymphomas) approximately 75%, decreases serum insulin-like growth factor (IGF)-1 and leptin levels, and induces apoptosis in immature (lymphoma-susceptible) thymocytes. In heterozygous p53-deficient (p53+/-) mice, CR or a one day/wk fast each significantly delay spontaneous tumor development (a mix of lymphomas, sarcomas, and epithelial tumors) and decreases serum IGF-1 and leptin levels, even when begun late in life. We have also reported similar effects in ApcMin mice. We have capitalized on the susceptibility of p53+/- mice to chronic, low-dose aromatic amine-induced bladder carcinogenesis to develop a model for evaluating bladder cancer prevention approaches. Using this model, in combination with mice overexpressing or deficient in IGF-1, we have established that IGF-1 mediates many, but not all, of the anti-cancer effects of CR. We have also used oligonucleotide microarrays, in addition to models of diet-induced obesity and treadmill exercise, to characterize diet-gene interactions underlying the effects of energy balance on cancer, and in particular identify genes linked to the diet or exercise response that are IGF-1 dependent.

1509 THE ROLE OF MAP KINASES IN METAL TOXICITY

A. R. Villalobos. *Environmental Medicine, University of Rochester, Rochester, NY.*

Mitogen-activated protein kinases (MAPKs) may mediate the cytotoxic responses and cytoprotective mechanisms elicited by metals, such as Zn, Cd, Cr, and As. The session will open with a review of the common and unique biochemical properties of MAPK family members, ERK1/2, ERK5, JNKs, and p38 proteins, activation of each MAPK cascade by selective stimuli, and the respective down stream targets in the context of their physiological function. A common cellular response to exposure to various metals is an altered redox state. The second talk will address direct activation of MAPKs by oxidants, such as hydrogen peroxide, and electrophiles, such as 4-hydroxy-2-nonenal (HNE), an end product of lipid peroxidation. A highlighted example of MAPKs as mediators of cytoprotective mechanisms recruited in response to oxidative stress will be HNE-induction of g-glutamyl transpeptidase via ERK1/2 and p38 and of glutamate-cysteine ligase via JNK, two responses critical to adaptive increases in GSH. The third talk will address MAPKs as mediators of cytotoxic responses triggered specifically by metal-induced oxidative stress. For example, Cr(VI) at toxic concentrations, via ERK1/2 and p38, upregulates p21 and cdc2 and causes degradation of cdc25C, leading to growth arrest at G2/M. The last two talks will address activation of MAPKs in response to metal exposure irrespective of changes in redox state, as observed with Zn and Cr(VI) in human airway epithelium. Zn induces activation of ERK1/2, JNK and p38 and the tyrosine kinase receptor, EGFR. Modulation of ERK1/2 and EGFR involves multiple levels of acti-

SOT | Society of Toxicology

The Toxicologist

Supplement to *Toxicological Sciences*

An Offical Journal of the Society of Toxicology

45th Annual Meeting and ToxExpo™

San Diego, California

OXFORD
UNIVERSITY PRESS

ISSN 1096-6080
Volume 90, Number 1, March 2006

www.toxsci.oupjournals.org

Preface

This issue of *The Toxicologist* is devoted to the abstracts of the presentations for the symposium, platform, poster discussion, workshop, and poster sessions of the 45th Annual Meeting of the Society of Toxicology, held at the San Diego Convention Center, San Diego, March 5–9, 2006.

An alphabetical Author Index, cross referencing the corresponding abstract number(s), begins on page 500.

The issue also contains a Keyword Index (by subject or chemical) of all the presentations, beginning on page 534.

The abstracts are reproduced as accepted by the Program Committee of the Society of Toxicology and appear in numerical sequence.

Copies of *The Toxicologist* are available at $45 each plus $5 postage and handling (U.S. funds) from:

Society of Toxicology
1821 Michael Faraday Drive, Suite 300
Reston, VA 20190

www.toxicology.org