using each procedure. The results obtained also indicate that repeated injection after twenty-four hours was accompanied by a decrease in the degree of analgesia produced. It was interesting to note that the repeated administration of morphine resulted in tolerance development only if animals were treated during the light phase when assessment was made using the hot plate and tail flick methods. However, animals developed tolerance using the front paw procedure at each specific hour of treatment. In the second experiment, four different groups of male Sprague-Dawley rats were injected with ethanol (3gm/kg) at 06:00, 10:00, 14:00, 18:00, 22:00, and at 02:00 hr for 2 consecutive days, and the degree of analgesia was measured after drug administration. The repeated injection of ethanol resulted in tolerance to the analgesic response only if animals were treated during the light phase using the front and hind paw procedures. The present results indicate the presence of chronotolernce to the analgesic effects of morphine and ethanol.(Supported by NIH Grant # RR 03020)

1491 NICOTINIC-RECEPTOR BLOCKADE AND THE EFFECTS OF ANATOXIN-A ON THE MOTOR ACTIVITY OF RATS: COMPARISON WITH NICOTINE.

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Anatoxin-a is produced by several species of freshwater cyanobacteria and has caused numerous poisoning episodes in terrestrial and aquatic wildlife, livestock and domestic animals. Anatoxin-a is also a potent nicotinic agonist in the nervous system and at the neuromuscular junction. There has been little research on the behavioral effects of anatoxin-a, and virtually no characterization of the role of nicotinic receptors. These experiments determined the effects and interactions of anatoxin-a and selective nicotinic-receptor antagonists on the motor activity of adult male Long Evans rats. Parallel studies included nicotine. Motor activity was evaluated in a commercial photocell chamber during 20-min sessions. Each experiment included groups of 9 rats that received a dose of anatoxin-a or nicotine, a dose of a nicotinic antagonist, and their combination. Each experiment also included a vehicle-control group. Doses of anatoxin-a and nicotine were 0.6 mg/kg and 2.5 mg/kg, respectively, and were administered s.c. 5-min prior to a test session. Nicotinic antagonists included dihydro-beta-ethroidine (DHBE, 10 mg/kg) and methyllycaconitine (MLA, 10 mg/kg). MLA was given s.c 15-min prior to testing and DHBE was given immediately before anatoxin-a or nicotine. Pretreatment with DHBE produced a transient blockade of the effect of nicotine, but did not block the effect of anatoxin-a. Pretreatment with MLA blocked the effect of anatoxin-a, but not that of nicotine. These results indicate anatoxin-a differs from nicotine in its site of action, most likely involving stimulation of alpha-7 nicotinic receptors in the nervous system.
This is an abstract of a proposed presentation; the information does not necessarily reflect Agency policy.

1492 BRAIN PGE2 CONCENTRATION IS ASSOCIATED WITH SUSCEPTIBILITY TO KAINATE-INDUCED SEIZURES.

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We have previously demonstrated that genetic deletion of cyclooxygenase (COX)-2, but not COX-1, the enzymes that metabolize arachidonic acid (AA) into prostanoids, can increase susceptibility to kainic acid (KA)-induced excitotoxicity. To further understand the mechanism of this increased susceptibility, we investigated the effect of chronic pharmacological inhibition of COX-2 on KA-induced excitotoxicity. Wild type mice were placed on a diet containing 0, 1000, or 3000 ppm celecoxib, a COX-2 selective inhibitor, for six weeks. At 12 weeks of age, mice were either euthanized by focused microwave irradiation of the brain or injected intraperitoneally with 10 mg/kg KA and euthanized 24 hours after injection. Celecoxib exposure did not alter mean group body weights over the course of treatment. A dose-dependent decrease in PGE2, a major COX-2 end product, was observed in the brains of celecoxib-exposed mice and COX-2 -/- mice (0 ppm = 9.2 ng/g; 1000 ppm = 7.2 ng/g (21%); 3000 ppm = 5.3 ng/g (41%); COX-2 -/- = 4.4 ng/g brain weight (52%)) with no effect of celecoxib treatment or genotype on brain levels of thromboxane B2 (TXB2), a COX-1 preferential end product. Kainate-induced seizure intensity, quantified by median Racine Seizure Scale (RSS), was increased in mice with decreased brain PGE2 concentration (0 ppm RSS =1; 1000 ppm RSS= 1; 3000 ppm RSS= 2; COX-2 -/- RSS= 3; Kruskal Wallace ANOVA p=0.008). This inverse relationship between PGE2 concentration and seizure intensity suggests that chronic inhibition of COX-2 may decrease the production of COX end products that regulate neuronal excitability. This data confirms our previous finding that genetic deletion of COX-2 increases susceptibility to KA-induced excitotoxicity and suggests that chronic exposure to COX-2 selective inhibitors may increase susceptibility to seizures and excitotoxicity. [Supported by the NIA IRP and NIH IRTA programs].

1493 NEUROPROTECTIVE ACTIONS OF PACAP38 IN MODELS OF DOPAMINERGIC TOXICITY.

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In this study we explore the possible neuroprotective actions of PACAP38 on dopamaine toxicity. PACAP38 (pituitary adenylyl cyclase activating polypeptide), a relative of VIP (vasoactive intestinal peptide), has been demonstrated to release growth factors and increase neurogenesis in the subventricular zone of the lateral ventricles (Mercer et al. 2004). Furthermore, endogenous expression of PAC1, a PACAP-specific receptor, is found in the substantia nigra pars compacta and acute direct injection of PACAP38 can protect nigral neurons against 6-OHDA toxicity (Reglodi et al. 2004). In our studies, a total dose of 1 mg/kg PACAP38 was administered to C57BL/6J retired breeder male mice via subcutaneous osmotic pumps over one week. Four weeks post-treatment, PACAP38 treated mice showed a 35% increase vesicular monoamine transporter-2 (VMAT2) in the striatum, but no change in tyrosine hydroxylase (TH) or dopamine transporter (DAT). Also, at two weeks post-PACAP38, a 56% elevation in vesicular uptake velocity of dopamine was observed along with a 19% increase in VMAT2 protein. Since we have shown that mice with genetic reduction of VMAT2 are more susceptible to methamphetamine- and MPTP-induced damage (Fumagalli et al 1997), we decided to test if PACAP38 is protective in these models. PACAP38 treatment 48 hours after MPTP attenuated some of the behavioral deficits of these mice and was able to reduce VMAT2 loss by 50%; results from methamphetamine studies are pending. While administering PACAP38 after a toxic challenge is effective, PACAP38 pretreatment may provide enhanced resistance to dopamine neurotoxicants and other oxidative challenges by elevating VMAT2 levels, thus reducing intracellular dopamine quinones. Since dopamine neurons are already vulnerable due to high basal levels of oxidative stress, reducing this load by increasing VMAT2 may also prolong the survival of these neurons in an unchallenged state as well.

1494 EXERCISE PROVIDES NEUROPROTECTION AGAINST KAINIC ACID TOXICITY THROUGH INDUCTION OF THE CHEMOKINE MCP-1 IN THE HIPPOCAMPUS OF C57BL/6J MICE.

S. A. Benkovic, K. Sriram, J. P. O'Callaghan and D. B. Miller. *TMBB, CDC-NIOSH, Morgantown, WV.*

Physical exercise affords protection to neurons exposed to the excitotoxicant kainic acid (KA). We previously observed attenuation in KA-induced argyrophilia and blood-brain barrier disruption following a 14-day regimen of forced walking in male C57BL/6J mice. Here, we investigated the role of microglial activation in the hippocampus, and the production of microglial-derived factors in the protective mechanism. Mice were assigned randomly to one of four experimental groups: saline, kainic acid, exercise + saline, exercise + KA. Forced walking was achieved in a motorized exercise wheel (6 rpm, 60 min duration, 4:00 PM daily). Mice were acclimated to the wheels for three days, exercised for 14 days, and given an intraperitoneal injection of KA (25 mg/kg). Control animals were not exercised, and received a comparable injection of saline. Following a 12-hour survival, animals were sacrificed and their brains were dissected into regions for RNA extraction and analysis of microglial markers and secretory products by RT-PCR. KA treatment caused a four-fold induction in hippocampal levels of the neurotrophic factor Gdnf, and a two-fold induction in Igf-1: bdnf levels were slightly but non-significantly elevated. Microglial markers, F4/80, Iba1, Mac-1, and p67Phox were unchanged between experimental groups. KA treatment caused a 3-fold induction in Il-1α and Il-6 levels, a 15-fold induction in Tnf-α levels, and an 8-fold induction in Mcp-1 that was increased to 23-fold by exercise pretreatment. Our data suggest the protective effects of exercise against excitotoxicity may occur through modulation of the neuroinflammatory response, and may be mediated through the chemokine Mcp-1. Subsequent experimentation will evaluate the protective effects of exercise in Mcp-1 knockout mice.
"The findings and conclusions in this report (abstract/presentation) have not been formally disseminated by the National Institute for Occupational Safety and Health and should not be construed to represent any agency determination or policy."

1495 SUSCEPTIBILITY TO 1-BROMOPROPANE EXPOSURE AND ALTERATION OF mRNA EXPRESSION IN RATS.

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The present study aimed to investigate the possible genes related with difference in susceptibility to 1-bromopropane (1-BP) exposure between two inbred strains of rat, F344 and Wistar Nagoya (WNA). Eighteen of 8wk old F344 or WNA male

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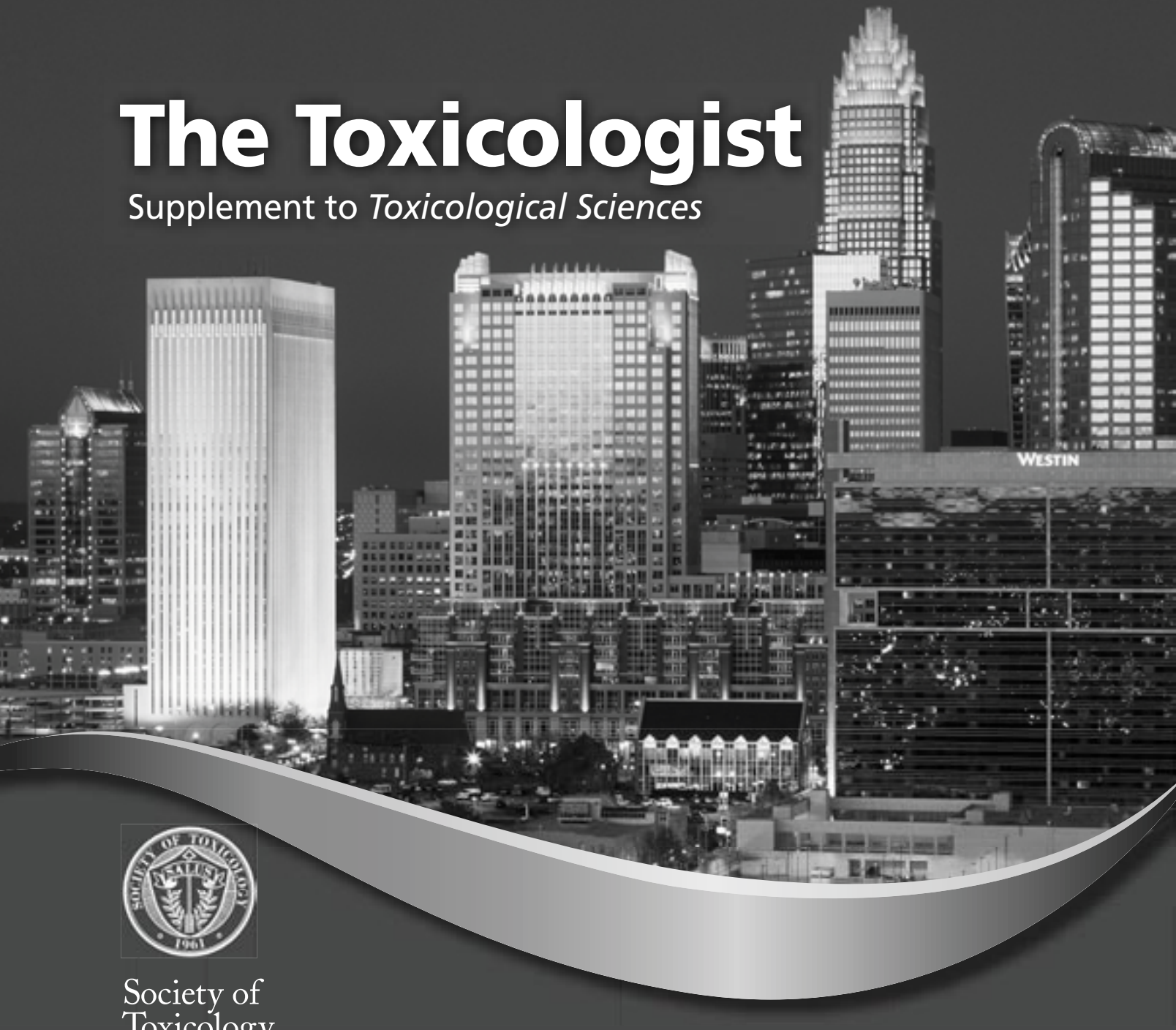

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Preface

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An alphabetical Author Index, cross referencing the corresponding abstract number(s), begins on page 449.

The issue also contains a Keyword Index (by subject or chemical) of all the presentations, beginning on page 480.

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