tants that increase BDNF expression offset excitotoxic damage (Bahr et al. Exp. Neurol. 174:37, 2002). Also of interest is that distinct compensatory events occur in response to the different toxic exposures. NMDA exposure leads to increases in HSP27 and HO-1, whereas these genes are reduced in the GD-slices. Low-level GD causes a 11-fold increase in IL-15, while it is reduced in the NMDA response. Perhaps compensatory pathways identified with microarrays can provide strategies with which to offset GD-induced vulnerability.

422 SIGNALING PATHWAYS ASSOCIATED WITH GLIOSIS CAN BE STUDIED USING A BRAIN SLICE PREPARATION.

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Damage to the CNS is characterized by activation of microglia and astroglia, a phenomenon termed reactive gliosis. These cellular reactions have been implicated in both regeneration and degeneration of the CNS. Damage-induced production of cytokines and chemokines has been linked to the initiation of gliosis using several injury models, including exposure to known neurotoxicants. The Janus kinase-signal transducers and activators of transcription (JAK-STAT) pathway is a downstream effector of cytokines and activation of this pathway is associated with gliosis. In particular, the transcription factor STAT3 is critical for astroglial response to CNS damage. Here, we used brain slices from mice treated with the dopaminergic neurotoxicant, 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP) to examine astroglial STAT3 activation responses. 12 hours post MPTP (12.5 mg/kg, s.c.) or saline treatment, C57Bl/6 female mice were sacrificed by decapitation and coronal slices of brain were prepared. Striatum was dissected and assayed for activated STAT-3 (Tyr705 phosphorylation). Phospho-STAT3 was present in slices from MPTP treated mice immediately following sacrifice while absent in control mice, recapitulating *in vivo* observations. These data suggest that activated STAT3 is preserved in brain slices. Striatal slices were then exposed to phosphate free oxygenated buffer for various times. After 45 minutes both MPTP treated and control striata expressed p-STAT3, indicating that MPTP induced phosphorylation is retained *ex vivo* and that STAT3 activation can also result from slice injury. Production of cytokines upstream of STAT3 was examined by RT-PCR. Messenger RNA for CNTF and IL-6 was not altered while mRNA for MCP-1 and LIF was increased. Finally we determined that AG490, a JAK inhibitor, and lavendustin A, a tyrosine kinase inhibitor, could diminish STAT3 phosphorylation in slices. These data suggest that activation of STAT3 is an early event in both toxicant and slice-induced glial activation. In addition, this investigation establishes the brain slice preparation method as a reliable model to examine reactive gliosis.

423 HEXANEDIONE (HD)-INDUCED CHANGES IN THE POLYMERIC AND MONOMERIC STATE OF RAT SPINAL CORD CYTOSKELETAL PROTEINS.

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Accumulating evidence now suggests that axon atrophy in PNS and CNS is the hallmark morphological feature of gamma-diketone neuropathy (e.g., Toxicology. Appl. Pharmacology 135: 58-66, 1995; 165: 127-140, 2000; in press, 2003). Adult axon caliber is maintained by interaction of the cytoskeletal polymer with a mobile pool of exchangeable NF proteins. This interaction can be studied by triton-extraction of nervous tissue followed by differential fractionation. We used this experimental approach to determine how HD intoxication affected NF subunit content in the triton-insoluble cytoskeletal polymer and the soluble monomeric fraction. Lumbar spinal cords from moderately affected HD-intoxicated rats (175 mg/kg/d x 101 days; 400 mg/kg/d x 26 days) or their age-matched controls were homogenized in triton buffer and subjected to differential centrifugation. The low-speed (15, 000g) triton-insoluble pellet (P1 or highly polymerized cytoskeleton), and the high-speed (100, 000g) triton-soluble pellet (P2, or limited NF polymer) and corresponding supernatant (S2, or triton-soluble NF monomer/oligomer) were retained for immunoblot analyses. Results show that, regardless of HD dose-rate, cytoskeletal proteins (tubulin, NF-L, -M and –H) in the P1 fraction were not significantly altered, whereas the NF subunit contents of the P2 and S2 fractions were substantially depleted. Studies with antibodies directed against phosphorylated (RT97) and nonphosphorylated (SMI32) epitopes on NF-H and measurements of corresponding subunit isoelectric point suggest that HD-induced changes in phosphorylation were not involved. These results are consistent with previous published findings regarding NF content in nervous tissue of HD-exposed rats and suggest that atrophy is related to depletion of exchangeable monomeric subunit in the S2 fraction with subsequent impairment of NF turnover. Supported by NIEHS grant ESO7912-7.

424 SUPRAPHYSIOLOGICAL LEVELS OF THE STRESS HORMONE CORTICOSTERONE ATTENUATE BLOOD-BRAIN BARRIER DISRUPTION AND MICROGLIAL ACTIVATION IN HIPPOCAMPUS OF C57BL/6J MICE TREATED WITH KAINIC ACID.

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Kainic acid intoxication in C57BL/6J mice causes neuronal damage and the activation of glial cells. Neurotoxicants can alter blood-brain barrier integrity, and the influx of blood-borne factors may contribute to the total toxicity profile. We evaluated the consequences of kainate treatment on the blood-brain barrier and microglial activation, and the ability of high levels of corticosterone to modulate pathology. Male mice were implanted with a corticosterone pellet (192 mg/kg/d) to mimic the sustained activation of the HPA axis associated with chronic stress, and allowed to recover for seven days. Control and implanted mice were injected intraperitoneally with saline or 25 mg/kg kainic acid, and sacrificed at 1, 3, 6, and 12 hours posttreatment. Kainate-induced seizures were scored at Stage 1 (Racine scale), and corticosterone pretreatment did not alter seizure activity. Analysis of hippocampal IgG levels by Western blotting revealed a kainate-induced breach of the blood-brain barrier, and subsequent influx of plasma-derived IgG by one hour, which continued to increase and achieved significant elevation at six hours posttreatment. Corticosterone pretreatment attenuated the kainate-induced influx of IgG at all time points. Immunohistochemical localization of IgG in hippocampal parenchyma paralleled blot data. Microglial activation following kainate treatment was evaluated by silver staining and revealed activated cells at one hour posttreatment. Staining with Isolectin B4 revealed numerous microglial cells throughout the hippocampal parenchyma at 12 hours posttreatment, and an attenuation in the quantity of microglia by corticosterone pretreatment. The interactions of chronic stress and chemical intoxication, and subsequent effects on neuroanatomy and physiology are complicated, and though many literature reports describe exacerbation of neurotoxicity by stress, our data suggest steroid treatment can be protective.

425 USE OF MAGNETIC RESONANCE IMAGING (MRI) TO EXAMINE MORPHINE-INDUCED INTRATHECAL GRANULOMAS.

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Continuous intrathecal (IT) delivery of morphine sulfate (MS) for 28 days can produce aseptic subdural extramedullary inflammatory masses (granulomas) localized at the catheter tip. To develop a non-invasive method of assessing the dynamics of granuloma formation and progression we investigated the use of MRI with gadolinium (Gd) enhancement. Beagle dogs were implanted with chronic intrathecal lumbar catheters and received MS infusions *via* vest mounted pumps for 28 days at a concentration known to produce granuloma formation (12.5 mg/ml, 0.96 ml/day). Animals were assessed for behavior and motor function twice daily. Prior to initiation of morphine infusion, baseline T1 and T2 weighted MRI scans were obtained with a Siemens Symphony 1.5 Tesla system while dogs were anesthetized with propofol. At 7-day intervals dogs underwent repeat MRI scans. If pathology was noted, additional imaging studies were conducted pre and post intravenous gadoversetamide (Optimark), 0.2 mmol/kg. On the day of the final scan, images were made pre and post IT injection of 1 ml of gadopentetate diglumine (Magnavist) 1:400 in saline prior to the intravenous Gd studies. Animals underwent necropsy within 24 hours of the final scan. Animals displaying severe side-effects prior to 28-days were sacrificed to prevent undue suffering. Repeat MRI scans with propofol anesthesia were well tolerated in dogs. There were no apparent abnormalities attributable to the MRI, propofol or Gd exposure. Serial saggittal and axial MRI imaging clearly displayed progression of a mass localized in the area of the catheter tip that was confirmed at necropsy. Intravenous Gd greatly enhanced differentiation of masses from spinal parenchyma. IT Gd displayed irregular distribution indicating probable alterations in cerebral spinal fluid flow patterns and thus morphine distribution. Physical signs were well correlated with the progression and localization of IT masses. MRI with Gd enhancement is a *via*ble method for evaluation of intrathecal mass development on dogs. Supported in part by DA-15353.

426 MOLECULAR ACTIONS OF ACRYLAMIDE (ACR) AT THE NERVE TERMINAL.

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We have provided evidence that nerve terminals in the CNS and PNS are primary sites of ACR action and that compromise of neurotransmission might mediate neurotoxicity (Neurotoxicology 23: 43-59, 2003; Toxicology. Appl. Pharmacology

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