Program#/Poster#: 63.16/Q10

Topic: C.11. Neurotoxicity, Inflammation, and Neuroprotection

Support: Intramural funding from CDC-NIOSH

Title: Gene expression profiling and pathway analyses reveal molecular signatures and relationships underlying enhanced methamphetamine neurotoxicity caused by protracted corticosterone exposure

Authors: K. A. KELLY, D. B. MILLER, *J. P. O'CALLAGHAN
NIOSH, Centers For Dis. Control and Prevention, MORGANTOWN, WV

Abstract: Damage to the CNS results in complex changes in molecular and cellular pathways associated with neuronal and glial responses at the sites of injury. Enhanced expression of proinflammatory cytokines and chemokines often accompanies injury-induced glial activation, including glial responses to neurotoxic insults. Previously, we documented a striatal neuroinflammatory response following nerve terminal damage due to acute exposure of mice to the dopaminergic neurotoxicant methamphetamine (METH), one that was markedly exacerbated by pretreatment with the stress hormone corticosterone (CORT). When mice were pretreated with chronic CORT, an exaggerated neuroinflammatory response (TNFα, IL6, chemokine (C-C motif) ligand 2 (CCL2), IL1β, leukemia inhibitory factor (LIF) and oncostatin M (OSM)) to METH was observed, an effect that was accompanied by exacerbated METH-induced astrogliosis (glial fibrillary acidic protein (GFAP)), microglial activation (Isolectin B) and dopaminergic neurotoxicity (Tyrosine Hydroxylase (TH)). To elucidate further changes associated with chronic CORT (1 week in drinking water) pretreatment, we examined gene expression profiles in the striatum at 12 and 24 hours after METH exposure of C57Bl6/J male mice (20 mg/kg, s.c.) to chronic CORT (400 mg/L) or vehicle treated mice. Using an Illumina MouseRef-8 BeadChip by Expression Analysis to assess gene expression after CORT and METH treatment followed by Ingenuity Pathway Analysis, we observed changes consistent with our previous findings. The top networks for chronic CORT and METH treated mice were inflammatory response, cell death, endocrine system development and function (with a score of 54) at 12h and inflammatory response, cell-to-cell signaling and interaction, cell death (with a score of 53) at 24h including focus molecules GFAP, LIF, suppressor of cytokine signaling 3 (SOCS3), S100 calcium binding protein B (S100B), signal transducer and activator of transcription 3 (STAT3) and TH. The top networks for METH treatment alone were cell death, nervous system development and function, cellular movement (with a score of 19) at 12h and behavior, cell signaling, molecular transport (with a score of 19) at 24h including focus molecules chemokine (C-X-C motif) ligand 2 (CXCL2), GFAP, S100B and serine proteinase inhibitor, clade A, member 3 (SERPINA3). Many of the focus molecules up- and down-regulated in this data set are related to astrogliosis and neuroinflammation. These data will

inform further investigation of the mechanisms of METH-induced dopaminergic neurotoxicity and provide the earliest biomarkers of neuroinflammation and glial activation responses.

Disclosures: K.A. Kelly: None. **D.B. Miller:** None. **J.P. O'Callaghan:** None.

Poster

063. Neuroprotective Mechanisms: Stem Cells and Glia

Location: Hall F-J

Time: Saturday, October 13, 2012, 1:00 PM - 5:00 PM

Program#/Poster#: 63.17/Q11

Topic: C.11. Neurotoxicity, Inflammation, and Neuroprotection

Support: Grant-in-Aid for Scientific Research (KAKENHI)

Title: PACAP suppresses retinal neuronal damage through modulation of the activation state of retinal microglia/macrophage

Authors: *T. NAKAMACHI[1,2], Y. WADA[2,3], T. SEKI[2,3], D. TSUCHIKAWA[2], M. HORI[2], M. TSUCHIDA[2], A. YOSHIKAWA[2], A. MATKOVITS[2], N. KAGAMI[2], N. IMAI[2], S. ARATA[1], S. SHIODA[2]
[1]Ctr. for Biotecnology, [2]Dept. of Anat., [3]Dept. of Ophthalmol., Showa Univ., Tokyo, Japan

Abstract: Pituitary
adenylate cyclase-activating polypeptide (PACAP) is a neuropeptide expressing central and peripheral nervous system. We have revealed that PACAP had a neuroprotective effect against N-methyl-D-aspartic acid (NMDA)-induced retinal injury. Recently, it was reported that increment of the number of retinal microglia/macrophages (RM/M) contributed to the neuroprotection on retinal injury. The aim of this study is to clarify the association between the retinoprotective effect of PACAP and RM/M on NMDA-induced retinal injury. In anesthetized adult male mouse (C57/BL6J) were injected NMDA (40 nmol) in 2 μL saline solution into the vitreous body by a 32G needle through the limbal sclera to a depth of 1 mm. PACAP38 at concentration of 10^{-8}, 10^{-10}, 10^{-12} M were co-treatment with NMDA. At 3days after injection, the number of RM/M and surviving retinal ganglion cells in NMDA and PACAP 10^{-10} M concentration co-treated retina were significantly higher than that of NMDA treated retina. Co-treatment with PACAP and PACAP receptor antagonist, PACAP6-38 suppressed the phenomenon. The numbers of RM/M and retinal ganglion cells were significantly correlated. By real time-PCR analysis, PACAP co-treatment with NMDA significantly elevated tgf-beta1 and il-10 mRNA level as a marker for