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Presentation Abstract

Program#/Poster#: 66.12/T9

Presentation Title: Using global gene expression profiling and pathway analysis to investigate kainic acid neurotoxicity and corticosterone neuroprotection in the C57BL/6J mouse hippocampus

Location: Hall F-J

Presentation time: Saturday, Oct 13, 2012, 4:00 PM - 5:00 PM

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Abstract: Systemic exposure to kainic acid (KA) causes seizures and damage in male C57BL/6J mouse hippocampus as evidenced by increases in GFAP, a biomarker of astrogliosis and Fluoro-Jade staining, a biomarker of neural injury. In our recent work exposure of mice to exogenous levels of corticosterone (CORT) sufficient to reduce the thymus and spleen weight by 70-80% provided substantial protection against the KA-induced hippocampal damage despite the continued rpesence of behavioral seizures. Here our aim was to use microarrays (Illumina, MouseRef-8 v2.0) and pathway analysis (Ingenuity) to characterize the time-related changes in the transcriptome of mice exposed to KA alone or KA-CORT. Male C57BL/6J (8 months of age) were implanted with time-release (100 mg/21 days, Innovative REsearch of America) pellets in a supramuscular cavity in the scapular area. After 7 days mice were given an i.p. injection of saline (SAL) or KA (25 mg/kg) and hippocampus was collected at 3, 6, 12 & 24 hrs post injection and kept at 80^{o}C until prepared for microarray analysis. Using >1.5-fold change and p-value<.01 there were significant transcriptome differences between mice given CORT or SAL; differentiall expressed (DE) genes included a number of known glucocorticoid-dependent genes including SULT1A1, PLIN4, SGK1 but no genes liked to the atroglia response (e.g., GFAP, SOCS3) were elevated and confirmed our previous finding of no CORT-induced hippocampal damage. The top network (score 47) identified by the bioinformatiocs analysis of the DE genes was Cellular Function and Maintenance, Cellular Assembly and Organization, Cellular Movement. The DE genes varied by time and group

when comparisons were made betwwen the SAL, KA & KA-CORT groups. In comparisons between the KA & SAL groups DE of genes concerned with transcription (FOS, FOSB, ARC, ANF238 were prominent at 3 and 6 hrs while those concerned with astrogliosis, inflammation and metalloproteinase inhibition (GFAP, CCL2, TIMP1, SOCS, SERPINA3, S100A11 were prominent at 12 & 24 hrs. Protracted treatment with CORT significantly altered the DE profile found with KA. Genes associated with astrogliosis, inflammation were down-regulated compared to KA and reflect the decrease in KA neurotoxicity engendered by prolonged CORT exposure. In addition a number of genes associated with protein folding (FKBP5) and the cellular stress response (SGK1) were upregulated. Additional bioinformatics analysis will provide insight into the molecular mechanism responsible for the neuroprotection afforded by CORT.

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

Keyword(s): CORTICOSTERONE

KAINIC ACID

GENE EXPRESSION

Support: HHS intramural support

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