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ROLE OF PROINFLAMMATORY CYTOKINES IN CHEMICALLY-INDUCED D OPAMINERGIC NEURODEGENERATION. Krishnan Sriram and James P. O'Callaghan; *Centers for Disease Control and Prevention-NIOSH, Morgantown, WV*

The pathogenic mechanisms underlying Parkinson's disease (PD) remain enigmatic. In an effort to identify early molecular events associated with PD, we profiled genomic and proteomic changes in the MPTP mouse model of PD. Specifically, we focused on the role of TNF- , IL-1 , IL-6 and MCP-1, since enhanced expression of these proinflammatory cytokines and chemokines have been found in association with glial cells of patients with PD. MPTP caused a time-dependent increase in the mRNA expression of these cytokines in the striatum, but not in the hippocampus, and their expression preceded striatal dopaminergic degeneration (loss of dopamine and tyrosine hydroxylase), activation of JAK/STAT3 pathway and astrogliosis (upregulation of GFAP). Deficiency of the IL-6 gene did not alter striatal nerve terminal loss, but attenuated astrogliosis. However, in transgenic mice lacking TNF receptors (TNFR-DKO), loss of striatal dopaminergic markers, phosphorylation of STAT3, upregulation of GFAP and astrocyte hypertrophy were nearly abolished. Interestingly, the lack of TNF receptors exacerbated hippocampal neuronal damage (increased Fluoro Jade-B staining and loss of MAP-2 immunoreactivity) after MPTP. These findings implicate a region-specific role for TNF- in the brain: a promoter of neurodegeneration in striatum and a protector against neurodegeneration in hippocampus. From a Parkinson's disease perspective, these findings are suggestive of a primary role for TNF- in the pathogenesis of this disorder. As deficiency of TNF receptors or IL-6 gene attenuated phosphorylation of JAK-STAT3 and upregulation of GFAP, the findings implicate these signaling pathways in upregulation of GFAP. Since the activation of these pathways are early events in MPTP neurotoxicity, they may serve as potential therapeutic targets for modulation of neuronal loss and/or glial response following dopaminergic neurodegeneration.

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DISSOCIATIONS BETWEEN PATHOGENESIS-BRAIN AND BRAIN-BEHAVIOR CORRELATIONS: IMPLICATIONS FOR IMAGING RESEARCH MR Herbert, DA Ziegler, N. Makris, PA Filipek, C. Deutsch, DN Kennedy, VS Caviness; *Center Morphometric Anal, MGH, Charlestown, MA & Shriver Center, Waltham, MA, UC Irvine, Irvine CA*

Brain development can be altered by many factors, including chemicals, hormones and cytokines, whose impact can vary in character and localization due to complexities of timing, dosage and state of the organism. Changes may include altered cell size, cell number, packing density, and arborization, which may yield detectable alterations in brain volumes. The distribution of such effects may, however, bear no systematic relationship to the organization of neural systems, so that the impact upon behavior may not illuminate the nature of the underlying disorder. Nevertheless, the distribution of volume changes may indicate selective vulnerability traceable to the timing and mechanisms of histogenetic events or injury, and provide a basis for formulating animal models for human disorders. In our whole brain MRI morphometric analyses of boys with high-functioning autism and developmental language disorder (DLD) we found non-uniform volume changes, regionalized radiate white matter enlargement and widespread cortical asymmetry shifts consistent with distributed neural systems disruptions and postnatal timing that could not have been detected had we chosen regions of interest *a priori* on the basis of the neurocognitive profiles in these disorders. *Conclusion:* Imaging studies seeking to detect the impact of chronic or low dose exposures should seek broadly distributed changes, and should avoid prematurely constraining toxicological inquiry with behaviorally driven hypotheses. *Support: NINDS NS02126, NS20489, Cure Autism Now Fdn.* Keywords: MRI, morphometry, neural systems

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NEUROMORPHOMETRICAL STUDY ON THE RADIOPROTECTIVE ROLE OF BETA-CAROTENE ON POSTNATALLY DEVELOPING MICE CEREBELLUM. A.L. Bhatia, Rashmi Sisodia & Manish Sharma *Radiation Biology Laboratory University of Rajasthan, Jaipur-302004; India*

The present study is an endeavor to explore the possible role of beta-carotene as an antioxidant against radiation induced free radicals in cerebellum of mice in early developing postnatal period. In mice, cerebellum develops mainly after birth up to three weeks in many respects. Swiss albino mice of different age groups (1 to 3 weeks) were selected from an inbred colony and divided in five groups in each age group. Mice in the first group were given only corn oil, which is used as a vehicle in the present experiment. Second group was taken as normal (sham irradiated and on treated), third group received only beta-carotene (30mg/kg. body wt.)Procured from sigma chemicals U.S.A, fourth group was exposed to 4 Gy of gamma radiation (control) by Theratron model B, 60Co beam therapy unit. Fifth group was exposed to 4Gy of gamma radiation after supplementation of beta-carotene (30mg/kg.b.wt) for two weeks (experimental). Mice were sacrificed on different post irradiation days (1, 3, 7, 15 and 30 days) after cervical dislocation and observed for neuromorphometrical evaluation after due procedure. A wide variation was noticed in various parameters except length and width of brain and width of cerebellum. A conspicuous protection has been noticed in the bodyweight as per the following order 2 weeks>1 weeks>3 weeks. The brain and cerebellum weight shows the protection in the following order 3>2>1 weeks. Late intervals showed lesser protection mainly due to recovery in the irradiated group. However, such recovery was not evident in number and volume of Purkinje cells, molecular and granular layers of irradiated mice when the