IL-1, TNF, IL-6). **Objective(s):** Characterize the time course and nature of cytokine-to-brain communication during an immune challenge. **Methods:** In Exp 1, LPS (ip, 96 ± 9 μg/kg) or saline were administered to conscious adult male rats, and changes in brain glucose metabolic rate were assessed 2 hr or 6 hr later with [^{18}]FDG. In Exp 2, in ten young (20-40 y.o.) healthy males with no psychiatric history we collected serial 15O-water PET brain scans, body temperature, ACTH, cortisol, TNF-a levels, and symptom questionnaires before and after double-blind placebo-controlled IV LPS (2 ng/kg) administration. **Results:** LPS, but not saline, induced a robust, fever by 3 hr. in both rats and humans. In Exp. 1, using Wilks-Lamda MANOVA there was a significant overall effect of LPS versus saline ($F = 5.81$, $p = 0.031$) with the largest metabolic increases in the temporal cortex (36%, $p = 0.009$), hippocampus (32%, $p = 0.017$) and thalamus (30%, $p = 0.015$) two hours after LPS. This effect was not present in the 6 hr group. In Exp. 2, 30-min. post-LPS-administration there were no biological changes nor subjective symptoms. However, using SPM analyses and Principle Components Analyses, significant increases in rCBF were found in the mid-brain/pons, medulla, hypothalamus, R-amygdala, thalamus and subcallosalarea and bilateral hippocampus, insula, prefrontal cortex, and caudate. **Conclusions:** This study demonstrates that a peripheral immune challenge activates both blood flow changes in anatomically specific regions in humans and in overlapping regions, metabolic changes in the rat. The thalamic and limbic regions impacted by this challenge have anatomic similarity to the brain regions implicated in neurodegenerative diseases, like Alzheimer's disease. This clinical challenge paradigm coupled with imaging provides one of the first demonstrations of the neuroanatomic substrates modulated by peripheral immune stimulation. Future studies may apply this challenge paradigm to specific psychiatric or neurologic illnesses where the pro-inflammatory cytokines effects on neurochemistry and function are implicated in the pathology of illness.

P4-224 THE IN VIVO CONTRIBUTION OF THE GLIAL CYTOKINE S100B TO AMYLOID-BETA-INDUCED NEUROINFLAMMATION AND NEURONAL DYSFUNCTION

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Background: S100B is an astrocyte-derived protein that is increased in Alzheimer's disease (AD) brain in regions of neuropathologic vulnerability. Cell-based and clinical studies have implicated S100B in the initiation and maintenance of a pathologic, glial-mediated pro-inflammatory state in the CNS. However, the relationship between S100B levels and susceptibility to AD-relevant neurologic damage *in vivo* has not been determined. **Objective:** We used S100B transgenic (Tg) and knockout (KO) mice to test the hypothesis that overexpression of S100B increases vulnerability to Aβ-induced neuroinflammation and neuronal dysfunction. **Methods:** A rapid and reproducible *in vivo* assay for Aβ-induced neuroinflammation that involves intracerebroventricular infusion of human Aβ1-42 was used. Mice infused with Aβ exhibit many cardinal features of human AD, including a robust glial activation/neuroinflammation response, synaptic damage and neuronal loss in the hippocampus, deficits in spatial learning, and Aβ plaques. S100B Tg, KO, and wild-type (WT) mice were infused with Aβ for 21 days, sacrificed at 60 days, and hippocampus taken for histochemical and biochemical measurements. **Results and Conclusions:** S100B Tg mice showed increased vulnerability to Aβ-induced neuropathology relative to either WT mice or S100B KO mice. Specifically, S100B Tg mice exhibited more robust glial activation and neuroinflammation, an increased level of nitrotyrosine (a marker of glial-induced neuronal damage), and a more pronounced loss of synaptic markers. Interestingly, S100B Tg mice showed no significant differences in Aβ plaque number or amyloid load compared to WT or KO mice, suggesting no correlation between amyloid burden and the neuroinflammatory/neuronal dysfunction responses. Altogether, our data are consistent with a model whereby S100B overexpression in AD enhances glial activation, and leads to an accelerated neuroinflammatory process that increases the severity of neuropathologic sequelae. (Supported in part by NIH grant AG20243; JMC was supported by NIH T32 AG00260, F30 NS46942, and a PhRMA fellowship).

P4-225 EFFECT OF TGF-β1 GENETIC VARIABILITY ON SMALL VESSEL ISCHEMIA AND VASCULAR DEMENTIA: THE HONOLULU-ASIA AGING STUDY

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Background: Cerebral ischemia can lead to local hypoxia, neurodegeneration and vascular dementia. Pro- and anti-inflammatory processes contribute the progression of vascular damage. Experimentally, the cytokine transforming growth factor-β1 (TGF-β1) has shown to protect neurons in ischemic events. The genetic variants that influence the protein level of this cytokine could modify the risk for vascular lesions and dementia. **Objective(s):** To examine the association of the polymorphism TGF-β1+29 (T → C) with vascular dementia (VaD) and ischemic lesions identified in autopsied brain tissue. **Methods:** Data are from the Honolulu-Asia Aging Study (HAAS) a dementia study of Japanese American men. As a part of the HAAS, subjects were invited to enroll in an autopsy program. We used a nested case-control sample of 293 dementia cases, including 99 cases of VaD, and 491 controls randomly selected to frequency match the cases for age. Dementia was assessed in 1991 and 1994 by a multistep protocol. VaD was diagnosed according to the California Alzheimer's Disease Diagnostic and Treatment Centers guidelines. Autopsy data on brain micro, small and large infarcts were available on 282 cases and controls. Blood samples for the genotype analysis were collected in 1991. Logistic regression was used to assess the odds ratio (OR) for VaD after adjustment for age, education and several vascular-related risk factors; the analyses for cerebral vascular lesions were adjusted for age at death, education and vascular-related risk factors. **Results:** Compared to the more common TT genotype the mutant allele C was associated with a reduced risk for VaD ($OR_{TC} = 0.28$, 95% confidence interval (CI) 0.09–0.91; $OR_{CC} = 0.28$, CI 0.09–0.89). Compared to the TT genotype, the CC genotype showed reduced levels of micro infarcts ($OR_{TC} = 0.87$, CI 0.43–1.75 and $OR_{CC} = 0.31$, CI 0.13–0.71) and small infarcts ($OR_{TC} = 0.58$, CI 0.31–1.09 and $OR_{CC} = 0.62$, CI 0.31–1.23). Large infarcts were not associated with any allelic variant of the TGF-β1+29 polymorphism. **Conclusions:** The T allele of the TGF-β1+29 polymorphism may reduce the risk for VaD. The anatomical basis for this association may be the reduction of the risk for small vessel ischemic events.

P4-226 C/T CONVERSION AFFECTS INTERLEUKIN 1A PROMOTER FUNCTION IN A HUMAN ASTROCYTE CELL LINE

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Background: Recently, an association of the interleukin-1A (-889, T/T) polymorphism with Alzheimer's disease has been reported, suggesting that this cytokine may play an important role in the development of the disease. **Objective(s):** In order to understand the mechanism, a study comparing the promoter function of IL-1A polymorphism (-889, TT) and wildtype (CC) has been performed. **Methods:** The effects of TT and CC on the transcriptional activity of IL-1α were analyzed by testing luciferase reporter activity in a transient transfected human astroglial cell line (SVG). **Results:** As expected, a 15% more increase in the TT promoter activity was observed over the CC promoter. Furthermore, both LPS and Aβ significantly enhanced the activity of TT promoter (2.5× stimulation by LPS and 2.3× stimulation