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Age-Dependent Cytokine Responses: Trimethyltin Hippocampal Injury in Wild-Type, *APOE* Knockout, and *APOE4* Mice

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In this study, the hippocampal neurotoxicant trimethyltin (TMT) was used to examine possible differential susceptibility associated with the apolipoprotein E genotype. Mice—wild type (C57BL6J), APOE knockout, and APOE4 transgenic—received either saline or TMT (2 mg/kg, ip) at either 21 days or 8 months of age. At both ages, similar mRNA levels were seen in the hippocampus across genotypes for ICAM-1, A20, and MAC-1. GFAP mRNA was higher in the *APOE* knockouts and *APOE4* as compared to wild-type mice. Within 24 h, TMT produced cell death of hippocampal dentate granule neurons and mild astrogliosis in all animals. In 21-day-old mice, TMT exposure significantly increased mRNA levels for ICAM-1 and MIP-1α in all genotypes. EB-22, GFAP, TNFα, and TGF-β1 levels were significantly elevated in both wild-type and *APOE* knockout mice following TMT. At 8 months of age, genotype specific differences were observed. mRNA levels for GFAP, TNFβ, TNFα, and MIP-1α were increased in both *APOE* knockout and *APOE4* mice compared to wild-type mice. TMT exposure significantly increased mRNA levels for GFAP and MIP-1α in all animals. TNFα mRNA levels were increased in wild-type and *APOE4* mice while EB22 mRNA levels were increased in both the *APOE* knockout and *APOE4* mice but not wild-type mice. These data suggest an age-dependent effect on both microglia early inflammatory responses to injury associated with the APOE genotype.

Key Words: apolipoprotein E; GFAP; EB22; TNFα; MIP-1α; TGF-β1.

INTRODUCTION

Alzheimer's disease (AD) is a devastating neurodegenerative disorder. The clinical features of this disease include progressive dementia involving memory, orientation, and language functions and a gradual loss of other components of higher cognitive function such as personality, judgment, problem solving, and visual-spatial and constructional abilities (Morris et al., 1989, Mirra et al., 1991). The pathogenesis of AD is characterized by neural injury that includes a sequence of cellular events leading to the formation of neurofibrillary tangles, neuritic plaques, and loss of synapses (see Katzman, 1986; Hyman, 1997 for review). In addition to the neuronal component, there is evidence of a role for ''inflammatory'' responses in the pathogenesis of AD (Hull et al., 1996; Mrak et al., 1995; Sheng et al., 1996; Unger, 1998). These responses are marked by astrocyte reactivity and microglia activation throughout the cortex (Egensperger et al., 1998; Unger et al., 1998). In particular, activated microglia are found to be clustered near amyloid plaques (Licastro et al., 1998; Griffin et al., 1995; Uchihara et al., 1995; Saitch et al., 1997) that contain other components such as β-amyloid protein, thrombin, and apolipoprotein E (McGeer et al., 1994). This data, in conjunction with the identified features of microglia as a macrophagelike

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