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TOWARD AN UNDERSTANDING OF ALZHEIMER'S DISEASE V: DOES CHRONIC STRESS PLAY A ROLE?

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Alzheimer's disease which currently affects 4 million people in the United States, has been neuropathologically identified by the presence of neuritic plaques. Accumulating evidence has implicated that deposition of a protein, called beta amyloid (ßA), may play a causative role in the deterioration of cognitive function characteristic of Alzheimer's disease. Nonetheless, the mere presence of beta amyloid deposition in the central nervous system does not invariably predict Alzheimer's disease. Consequently, one major question that remains to be answered is what are the precipitating events that lead to beta amyloid-induced neuropathology. Recently, a study done by Dornan, Kang, McCampbell, and Kang (Neuroreport, 1993) reported a dramatic effect on the acquisition of spatial learning in the rat following bilateral injections of beta amyloid and ibotenic acid into the hippocampus. In that study, they speculated that the neurotoxic and behavioral effects observed were the result of a synergistic effect of ibotenic acid and beta amyloid which lead to an increase in calcium influx known to be neurotoxic to cells. It is noteworthy that glucocorticoids (stress hormones) released from the adrenal cortex also work via calcium channels and have been shown to be toxic to hippocampal neurons. Therefore, one possibility is that chronic stress, which releases glucocorticoids and increases calcium influx, may precipitate beta amyloid neurotoxicity. In an initial attempt to evaluate the interaction between beta amyloid and glucocorticoids, a preliminary pilot project was done to assess the effects of bilateral injections into the hippocampus on the acquisition of spatial learning in the rat. Two groups were utilized: group 1, 1 ml subcutaneous cortisol (7 mg/ml) injections and intrahippocampal injections of .5 microliter per side of ßA (1-42); group 2, adrenalectomized and intrahippocampal injections of .5 microliter per side of ßA (1-42). These groups were compared to two groups from the Dornan, Kang, McCampbell, and Kang study: group 1, ibotenic acid bilaterally injected into the hippocampus (25 nmol/side); group 2, bilateral hippocampal injections of saline. After adequate recovery time, spatial learning was assessed in each animal. A partially baited 8-arm radial arm maze (RAM) was used as the testing apparatus. Each subject was assigned one of four maze orientations. At the beginning of the RAM test, each animal was placed in the center of the maze and permitted to choose among the arms until it either found all bait or until 10 minutes had elapsed. Each subject was tested once daily for two weeks. After two weeks of having five baited arms, the configuration was then changed to have only two baited arms for an additional week. The number of arms revisited (total errors), repeated entry into previously baited arms (correct errors), entry into arms which were never baited (reference memory error), and repeated entry into unbaited arms (incorrect errors) were all recorded and analyzed by an ANOVA. The results of this study will be presented at the conference.