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THE EFFECTS OF ICV INJECTIONS OF AF64A AND STRESS ON THE ACQUISITION AND RETENTION OF A SPATIAL TASK IN MALE RATS

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Alzheimer's Disease (AD) is a neurodegenerative disorder which affects primarily the septal hippocampal pathway. AD is broadly characterized by a global and progressive deterioration of memory, cognition, and personality, with memory impairment being the most prominent feature of the early stages of the disease. Neuropathologically, it is manifested by the degeneration of the septohippocampal pathway, presumably due to the accumulation of beta amyloid (β A) protein deposits. The degeneration results in a dramatic decline in acetylcholine (ACh) levels. Consequently, AD has been theorized to be a disease of the cholinergic system, and therefore treatment strategies have focused on ways to increase ACh levels in the brain. Currently, however, there is no adequate animal model of AD available on which to test experimental compounds. In our laboratory we have taken two approaches toward the development of an animal model of AD. One approach has focused on the toxicity of β A. We have previously reported that bilateral injections of β A into the hippocampus exacerbates excitotoxic damage to the hippocampal area caused by a subthreshold dose of ibotenic acid. More recently, we have shown similar effects of β A in animals treated chronically with stress levels of glucocorticoids. Another approach is to mimic the degeneration of the acetylcholinergic fibers projecting to the hippocampus, and determine how the loss of these fibers affects memory and learning in the rat. A study by Hörtnegl et al (1993) demonstrated that glucocorticoids potentiate the neurotoxicity induced by injections of the relatively selective neurotoxin, AF64A. In the present study we will attempt to expand on these results, using a behavioral test (the Morris Water Maze- MWM) to determine the extent of changes in learning and memory. Rats received either corticosterone or sesame oil injections subcutaneously for a week prior to surgery. Rats were then injected bilaterally into the ventricles with either 1 nmol of AF64A per side or a control injection of the vehicle. After a two week recovery period, all animals were tested using the MWM task. There is a potential problem with using AF64A, due to the recent controversy regarding its selectivity to ACh. Therefore, we are doing a related study (also presented at this conference) using another selective ACh toxin called Saporin. The same behavioral tests will be performed, and the results of the tests will be compared and presented at the conference.