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An Animal Model of Alzheimer's: The Use of the Neurotoxin AF64A in Combination with Glucocorticoids to Differentiate the Importance of Cholinergic Pathways in Learning and Memory

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AN ANIMAL MODEL OF ALZHEIMER'S: THE USE OF THE NEUROTOXIN AF64A IN COMBINATION WITH GLUCOCORTICOIDS TO DIFFERENTIATE THE IMPORTANCE OF CHOLINERGIC PATHWAYS IN LEARNING AND MEMORY.

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There are approximately four million patients with Alzheimer's Disease (AD) in America today, with about 100,000 new cases being diagnosed every year. AD patients exhibit a prolonged loss of cognitive function, with learning and memory being among the first faculties to be affected. The pathological hallmarks of AD include senile plaques, comprised of the protein β-Amyloid. It is hypothesized that the aggregation of the β A protein into senile plaques in areas involved in learning and memory- such as the hippocampus- either causes the deficits seen in AD or acts synergistically to render the brain more vulnerable to insult. Previous efforts by our lab combining a neurotoxin with β A in the rat have demonstrated this, as well as β A in combination with the stress hormone corticosterone, which has been thought to exacerbate hippocampal damage in high levels. The deficits, however, have not been consistent. As an animal model of AD necessitates the dependability of these deficits, another possibility is being explored. The neurotransmitter system affected first and foremost in AD is the cholinergic system of the septohippocampal pathway. This is evidenced by a decrease of cholinergic markers such as choline acetyl transferase in AD brains. Much attention has been focused on the possibility of increasing the amounts of these cholinergic markers as a treatment for AD. The same premise has also been applied to the development of an animal model: a recent study by Hortnagl et al has demonstrated that intraventricular injections of a neurotoxic choline analog AF64A in combination with chronic glucocorticoid administration results in a decrease of cholinergic markers. This study, however, did no assessment to determine whether there were any resulting behavioral effects. We will attempt to expand on the Hortnagl study by assessing the effects on spatial learning in rats that have received injections of the neurotoxin AF64A and in combination with chronic stress. The Morris Water Maze will be used to test for behavioral deficits. The results of this study will be compared to another study at this conference which utilizes a highly selective cholinergic immunotoxin.