Modeling Alzheimer’s disease in mice by selectively lesioning the cholinergic basal forebrain

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Introduction

The degree of degeneration in the cholinergic basal forebrain (CBF) has been shown to correlate with the degree of dementia in Alzheimer’s disease (AD) patients (1, 2). This pathological feature of AD has been successfully modeled in rats using the immunotoxin 125I-goD Carlson (15-eps) which selectively kills CBF neurons after intrahippocampal injection (3, 4). In order to extend this approach to the mouse, the lesioning of the mouse CBF was performed. The lesioning of the mouse CBF was performed in the present study to characterize, behaviorally and histologically, the effectiveness of mu-p75-saporin in the present study to characterize, behaviorally and histologically, the effectiveness of mu-p75-saporin in the present study.

Results - Conditioned Fear

Passive avoidance learning in C57BL/J mice that received saline (SS), 1.88μg of toxin (LT), or 3.76μg of toxin (HT). Results: Both the low and high toxin groups showed significantly less freezing in the contextual fear task (CFT). The low and high toxin groups exhibited the same amount of freezing behavior as control mice in the cued fear conditioning task.

Summary of conditioned fear results: The mice that received toxin were impaired in the contextual fear task but had no impairment in the cued fear task.

Results - Accelerating Rotarod

Accelerating rotarod performance in saline and toxin injected mice.

Summary of rotarod results: The mice that received 3.76μg of toxin were impaired slightly in their motor coordination.

Histology - AchE

Control Low toxin High toxin

Hippocampus

Cortex

Results: Loss of fiber density in the target areas - hippocampus and cortex.

Immunohistochemistry

A) Purkinje Cells

B) Medial septum

Results: A) No loss of p75 Purkinje cells seen in the cerebellum. B) Intact GABAergic neurons seen in the medial septum and diagonal band area.

Conclusions and Summary

1. Injection of the immunotoxin, mu-p75 saporin, into the ventricular system did not cause any change in the spontaneous motor activity of the mice.

2. Injection of 1.88μg or 3.76μg of mu-p75 saporin caused a deficit in contextual fear conditioning, a task that is mediated by both hippocampal and amygdalar function. However, the low or high dose of toxin had no effect on the cued fear conditioning task, a task that is mediated by the amygdala. These data suggest that the toxin has disrupted the cholinergic innervation of the hippocampus but not the amygdala.

3. Injection of 3.76μg mu-p75 saporin impaired passive avoidance learning.

4. The rotarod experiment results suggest that the mice injected with 3.76μg of mu-p75 saporin had impaired motor coordination.

5. The histology results show a dose dependent loss of fibers in the cortex and hippocampus.

6. Purkinje cells in the cerebellum were not lesioned by the toxin.

7. GABAergic neurons are still intact in the medial septum and DB.

8. The present findings contribute to the development of the mouse model of AD. Future studies will more fully establish the relationships between immunotoxin dose, lesion extent, and behavioral impairment.

References


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