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Research report

Age-progressing cognitive impairments and neuropathology in transgenic CRND8 mice

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Abstract

Patients with Alzheimer's disease suffer from progressive cognitive impairments and show distinct post-mortem neuropathology, including β-amyloid plaques. Transgenic (Tg) CRND8 mice carry a mutated human amyloid precursor protein gene and show age-related increases in β-amyloid production and plaque deposition. It was previously reported that during the early stages of plaque deposition, Tg CRND8 mice demonstrated Morris maze impairments. However, it is unknown if Tg mice would be impaired at an earlier age prior to plaque deposition or more impaired at a later age with more extensive plaque deposition. In the current study, we describe Tg CRND8 age-progressing β-amyloid neuropathology and cognitive abilities in greater detail.

At all ages, Tg mice showed normal short-term memory in the Y-maze. Pre-plaque Tg and age-matched Non-Tg mice did not differ in learning the spatial Morris water maze. However, both early and late plaque Tg mice showed impairments during acquisition. In addition, although early plaque Tg mice performed well in the probe trial, late plaque Tg mice demonstrated impaired probe trial performance. Therefore compared to their Non-Tg littermates, Tg CRND8 mice demonstrate cognitive impairments that progressed with age and seemed to coincide with the onset of β-amyloid plaque deposition.

Keywords: Amyloid burden; Locomotor activity; Open field; Rota-rod; Reference memory; Novelty; Recognition; Sandwich immunoassay; Immunohistochemistry

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1. Introduction

Alzheimer's disease (AD) is the most common form of dementia among people over the age of 65 [12], with AD patients suffering from progressive loss of memory function and cognitive abilities [34]. AD is confirmed post-mortem by the presence of distinct neuropathological hallmarks, including senile plaques, neurofibrillary tangles, and neuronal cell loss, all of which progress with age. The exact causes of AD are unknown [3,33], but accumulating evidence suggests the involvement of β-amyloid (Aβ) peptides. Aβ peptides are produced by proteolytic cleavage of the amyloid precursor protein (APP) and $A\beta_{42}$ is the major constituent of senile plaques [27,33]. Furthermore, familial Alzheimer's disease (FAD) mutations of the APP, presenilin (PS) 1 and PS2 genes increase $A\beta_{42}$ production and lead to early-onset familial AD [31].

Several FAD mutations in human APP, PS1 and PS2 genes have been successfully over-expressed in mice, either alone or in combination (e.g., Tg2576: [17], PDAPP: [13]). APP FAD transgenic mouse models (with APP expression alone or together with PS1 or PS2 FAD mutations) show progressive, age-related increases in Aβ production, amyloid plaque pathology, astrogliosis, microgliosis and dystrophic neurites that are similar to what has been observed in AD patients. However, it is important to note that these mouse models of AD do not show certain AD-related pathological hallmarks, such as neurofibrillary tangles or substantial neuronal loss; hence, these mice model only certain aspects of the neuropathology that characterizes AD in humans [4,14,15].

As a cardinal feature of AD in humans, genetic mouse models of AD-like neuropathology should also show a progressive, age-related impairment in cognitive function [2,20]. Indeed, many studies have reported a progressive, age-related decline in certain aspects of cognitive function in transgenic mice expressing FAD mutations in the human APP gene with or without FAD mutated PS1 or PS2 genes [2,14,20]. The presence of progressive age-related cognitive impairments that parallel the progressive age-related neuropathology present in these models suggests that some aspect(s) of the amyloid neuropathology may be causing the decline in cognitive abilities.

Among studies which demonstrated progressive age-related impairments in certain cognitive measures in various transgenic AD mouse models displaying amyloid neuropathology, several reported that the impairments developed after an age at which plaque deposition had begun (e.g., PS1APP [1,29]; Tg2576 [5,8,10,28]; PDAPP [6,11]; APP23 [23]; PS2APP [30]), while others have demonstrated that the impairments preceded the onset of amyloid plaque deposition (e.g., Tg2576 [17,25,36]; PDAPP [18]; APP23 [35]; PS1Tg2576 [10]). Additionally, there have been reports that cognitive impairments were independent of age, either present at all ages tested regardless of pathology (e.g., TgCRND8 [19]), or not present at any of the ages tested (e.g., Tg2576 [24]; APPswe [32]). Overall, the relationship between amyloid neuropathology and cognition in transgenic AD mouse models is complex and requires further study.

One mouse model of AD-like amyloid neuropathology is the transgenic (Tg) CRND8 mouse. These mice over-express an APP gene containing the Swedish (K670N and M671L) and the Indiana (V717F) FAD mutations and show an age-related increase in Aβ production, as well as an early onset of plaque deposition in the cortex and hippocampus [7]. Up to 8 weeks of age, Tg CRND8 mice have elevated levels of $A\beta_{40}$ and $A\beta_{42}$, but no plaque deposition. From approximately 9 weeks of age, plaque deposition begins and progresses in these mice such that by 16 weeks, all Tg mice show multiple plaque deposits. Although Chishti et al. [7] provided a description of plaques in Tg mice as old as 32 weeks, quantification of the progression of Aβ plaque burden across a wider range of ages was not presented. In addition, it is not known how levels of cortical Aβ change after 26 weeks of age or how plasma Aβ levels change with age in Tg CRND8 mice.

Tg CRND8 mice have also demonstrated cognitive impairments [19] and abnormalities in synaptic plasticity [21] that seemed to be independent of age. At several ages after plaque deposition had begun (11–23 weeks), Tg CRND8 mice displayed impairments in the spatial version of the Morris water maze [7,19]. Since these were the only ages examined, it is not known if Tg CRND8 mice would show similar impairments at an earlier age, prior to plaque deposition. Further, it is also unknown if the Tg CRND8 Morris maze impairments are progressive in nature, such that at a later age when plaque deposition is more extensive in these mice, the cognitive impairments would be more severe than those seen in pre- or early plaque mice. Moreover, the Janus et al. [19] study was a longitudinal study (i.e., the mice were repeatedly tested in the same task at each age), allowing for the possibility that performance at the later ages may have been influenced by previous testing experiences in the maze.

The current study sought to replicate and, more importantly, extend the neuropathological and behavioral abnormalities observed in Tg CRND8 mice. By examining a wider range of ages (pre-plaque through late plaque; 6–50 weeks) and using a cross-sectional design (i.e., different mice were tested at different ages), we set out to characterize the progression of Aβ-related neuropathology and to determine if the spatial Morris maze impairments previously reported in early plaque Tg CRND8 mice were present prior to plaque deposition and progressed with age. In addition, locomotor activity, accelerating rota-rod performance, and short-term memory in the Y-maze were assessed in these mice throughout the age range.

2. Methods

2.1. Subjects

Tg and Non-Tg CRND8 mice were bred at the Schering-Plough Research Institute in Milan, Italy (for immunohistochemistry) or