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Detecting spatial memory deficits beyond blindness in tg2576 Alzheimer mice

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Abstract

The retinal degeneration *Pde6b*^{rd1} (*rd*) mutation can be a major pitfall in behavioral studies using tg2576 mice bred on a B6:SJL genetic background, 1 of the most widely used models of Alzheimer's disease. After a pilot study in wild type mice, performance of 8- and 16-month-old tg2576 mice were assessed in several behavioral tasks with the challenge of selecting 1 or more task(s) showing robust memory deficits on this genetic background. Water maze acquisition was impossible in *rd* homozygotes, whereas Y-maze alternation, object recognition, and olfactory discrimination were unaffected by both the transgene and the *rd* mutation. Spatial memory retention of 8- and 16-month-old tg2576 mice, however, was dramatically affected independently of the *rd* mutation when mice had to recognize a spatial configuration of objects or to perform the Barnes maze. Thus, the latter tasks appear extremely useful to evaluate spatial memory deficits and to test cognitive therapies in tg2576 mice and other mouse models bred on a background susceptible to visual impairment.

Keywords: Alzheimer disease; APP transgenic mice; Object location; Recognition memory; Barnes maze; Spatial memory; Vision; Blind mice; Retinal degeneration; Genetic background; B6SJL mice

1. Introduction

Alzheimer's disease (AD) is associated with a progressive impairment of several aspects of cognition, including spatial disorientation and episodic memory failures, as well as recognition and olfactory memory deficits (Buck et al., 1997; Kalová et al., 2005; Mesholam et al., 1998). The neuropathology of AD is characterized by amyloid plaques, which are extracellular deposits of β-amyloid peptide (Aβ), and neurofibrillary tangles. Less than 10% of the patients bear the familial form of AD caused by mutations on amyloid protein precursor (*APP*), *PS1*, or *PS2* genes, whereas the remaining majority of the patients are affected by the sporadic form of AD which depends on complex interactions between environmental and genetic risk factors. As most familial AD mutations, the "Swedish" double mutation of the *APP* gene leads to an abnormal cleavage of APP resulting in increased production of Aβ. One of the first APP transgenic models of AD is the tg2576 mouse which overexpresses this mutation (Hsiao et al., 1996). It is now widely used in fundamental AD research and therapeutic development. Tg2576 mice show a rapid increase in cerebral Aβ starting at an age of 6–7 months; usually, amyloid plaques deposition are found in the hippocampus and the cortex 3 to 6 months later (Kawarabayashi et al., 2001). Tg2576 mice also develop age-dependent spatial reference memory deficits in the Morris water maze, although the age

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of onset may vary from 3 to 12 months depending on the study (Hsiao et al., 1996; King et al., 1999). Memory deficits were confirmed in a wide variety of spatial tasks including Barnes-maze and spatial alternation tasks, as well as contextual and social memory tasks (Chapman et al., 1999; Deacon et al., 2009; Jacobsen et al., 2006; Middei et al., 2004; Ognibene et al., 2005). Deficits in spatial novelty tasks and preservation of object recognition performance, even at old ages, have been consistently reported (Good et al., 2007; Hale and Good, 2005; Ognibene et al., 2005). The tg2576 model, however, has also generated inconsistent results in several of the aforementioned spatial tasks (Deacon et al., 2008; Holcomb et al., 1999; King et al., 1999). In addition, some of these studies reported high within-group variability in both tg2576 and wild type (wt) littermates, thereby limiting the strength of the behavioral findings and even questioning the validity of this model (Deacon et al., 2008). The presence of the recessive retinal degeneration allele *Pde6b*^{rd1} (*rd*) in the B6:SJL genetic background of most available wt/tg2576 cohorts might, at least partly, explain the lack of consistency and behavioral variability. Most rods degenerate within 7 weeks of age in homozygous *rd* mice, whereas degeneration of the cones is much slower (Bowes et al., 1990; Carter-Dawson et al., 1978). Thus, *rd* carrying inbred strains, such as the SJL strain, show a dramatic visual deficit by 7–9 weeks of age, which deeply impairs their performance in tasks requiring visual guidance (Brown and Wong, 2007; Clapcote et al., 2005).

The challenge of the current work was to identify some tasks demonstrating robust memory deficits that are not affected by the *rd* mutation in tg2576 mice bred on a B6:SJL genetic background. In a first pilot experiment, we tested a cohort of 11-, 17-, and 21-month-old wt mice in a battery of tasks presumably impaired in tg2576 mice (water-maze, Barnes-maze, Y-maze, and spatial and object recognition tasks). Our aim was to select tasks demonstrating good performance and low variability in a B6:SJL background population made up of a majority of homozygous *rd* carriers. In a second study, these tasks were used to assess memory performance in a vast cohort of wt versus tg2576 mice of 2 ages (8 and 16 months). After genotyping of all mice, the data were specifically reanalyzed to determine the impact of the *rd* mutation on the performance of tg2576 and wt mice.

2. Methods

2.1. Animals

We used tg2576 female mice which express the transgene coding for the 695-amino acid human APP isoform containing the double Swedish mutation (K670N, M671L; Hsiao et al., 1996) and their wt female littermates. Our breeding colony (Bayer Pharma AG, Wuppertal, Germany) is maintained on a B6:SJL hybrid genetic background by mating hemizygous males with B6SJLF1 females. Our cohorts were composed of sisters from a limited number of litters (3–4 per age for the wt cohort; 14–15 per age for the transgenic (tg)/wt cohort). We chose females because they can be maintained in social groups until 2 weeks before the start of the testing period, as opposed to males which are quite aggressive under the same housing conditions. The first cohort consisted of wt mice only, which were 11, 17, and 21 months old at the beginning of the study (n = 10–13 per group). The second cohort consisted of tg2576 and wt littermates which were 8 and 16 months old at the beginning of the study (n = 11–14 per group). We also report here the results of a pilot study on 5-month-old tg2576 female mice (n = 14) tested in the object exploration paradigm, but not genotyped for *rd*. Mice were housed individually in transparent cages (22 × 20 × 14 cm) under controlled temperature (22 ± 1 °C) and a 12/12 hours light/dark cycle (lights on at 7:00 AM). Food and water was available ad libitum unless indicated otherwise. Paper towels were provided for nesting and a few food pellets were dropped inside the cage (in addition to those present in the cage cover). According to our experience, these conditions contribute to successful reduction of mortality. All experimental procedures were conducted in conformity with the institutional guidelines (council directive 87/848, October 19, 1987, Ministère de l'agriculture et de la Forêt, Service Vétérinaire de la Santé et de la Protection Animale; National Institutes of Health publication, 86–23, revised 1985). Official permission references for animal experimentation were 67–292 for C.M. and 67–215 for J.-C.C.; N.Y. was under their responsibility. Reference of official permission for holding genetically modified organisms (tg2576) was 5016 CA-II.

2.2. Protocol of the wt cohort pilot study

2.2.1. Locomotor activity test

Two weeks after their arrival at the laboratory, the wt cohort was tested in an actimetric device to evaluate general activity during habituation to a novel environment. The mice were placed individually in large transparent cages (42 × 26 × 15 cm^3) adapted to the testing device. Two infrared light beams were targeted on 2 photocells, 2.5 cm above the cage floor level and 28 cm apart. The number of longitudinal cage crossings was recorded from 11:00 AM to 5:00 PM.

2.2.2. Spatial novelty and object recognition tasks

Three days after the activity test, the wt cohort was tested in an object exploration paradigm, which is based on the spontaneous tendency of mice to explore preferentially new objects (object recognition) or objects moved to a new location (spatial novelty). Object recognition and spatial novelty tasks were performed in a Plexiglas open field (52 × 52 cm) with black walls (40 cm high) and a white floor divided into 25 equal squares by black lines. A striped card was fixed against a wall. The device was illuminated by an indirect halogen light (open field center: 40 lux) and a radio played a background noise 2.30 m from the device