Behavioural Brain Research 260 (2014) 111–118

Contents lists available at ScienceDirect

Behavioural Brain Research

journal homepage: www.elsevier.com/locate/bbr

Research report

Novel behavioural characteristics of female $APP_{Swe}/PS1\Delta E9$ double transgenic mice

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HIGHLIGHTS

- Characterisation of novel behaviours of APPxPS1 transgenic female mice.
- APPxPS1 female mice demonstrate spatial memory deficit in cheeseboard task.
- APPxPS1 females show task-dependent hyperlocomotor and anxiolytic-like behaviour.
- Unaltered sensorimotor gating and associative learning and memory of APPxPS1 mice.

ARTICLE INFO

Article history:
Received 22 October 2013
Received in revised form
19 November 2013
Accepted 25 November 2013
Available online 4 December 2013

Keywords:
Alzheimer's disease
Transgenic $APP_{Swe}/PS1\Delta E9$ mice
Behaviour
Social recognition memory
Sensorimotor gating
Cheeseboard

ABSTRACT

Murine models are commonly used to evaluate progression of Alzheimer's disease. $APP_{Swe}/PS1\Delta E9$ (APPxPS1) mice have previously been reported to demonstrate impaired learning and memory in the Morris water maze test. However, this paradigm introduces a variety of behaviours that may confound performance of the mice, thus an alternative was sought. A battery of behavioural tests (light–dark test, elevated plus maze, novel object recognition task, social recognition test, cheeseboard task and prepulse inhibition) was used to investigate various behavioural and cognitive domains with relevance to Alzheimer's disease. We found 9-month old female APPxPS1 mice exhibited impaired spatial memory in the reversal cheeseboard task. In addition, task-dependent hyperlocomotion and anxiolytic-like behaviours were observed in the light–dark test. Female APPxPS1 demonstrated intact object recognition memory and sensorimotor gating was not significantly decreased compared to control mice except for one particular interstimulus interval. The social recognition test failed to detect preference for social novelty in control females. In conclusion, this is the first study to describe a memory deficit in female APPxPS1 mice in the hidden cheeseboard task. Transgenic females also exhibited task-dependent reduction in anxiety behaviours and hyperlocomotion. These novel findings enhance our understanding of the behavioural phenotype of APPxPS1 females and present the cheeseboard as a valid alternative to other established spatial memory tests. Furthermore, the task-dependency of some of our findings suggests that behavioural profiling of APPxPS1 transgenic mice should be assessed using a variety of behavioural paradigms.

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1. Introduction

Alzheimer's disease (AD) is the most prevalent form of dementia. Post-mortem brain tissue of AD patients is characterised by amyloid-β peptide (Aβ) aggregation causing plaques and tau protein hyperphosphorylation, the latter being associated with neurofibrillary tangle formation (reviewed in Ref. [1]). AD patients exhibit behavioural and cognitive symptoms such as social withdrawal, deficits in language comprehension, and severe cognitive decline of short-term and long-term memory including the inability to recognise friends and relatives [2,3].

AD is classified as two subtypes: (1) sporadic AD (late onset) is the most common form of AD and results from a complex interaction of various environmental risk factors and susceptibility genes (e.g. *APOE*) [4]; and (2) familial AD (early onset, autosomal dominant), which accounts for <10% of all AD cases [5] and is caused by mutations in one of three genes: amyloid precursor protein (*APP*),

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http://dx.doi.org/10.1016/j.bbr.2013.11.046

presenilin 1 (*PS1*) or presenilin 2 (*PS2*) [6]. Transgenic mouse models of familial AD are commonly used to investigate progression of AD. Co-expression of mutant *APP* and *PS1* in double transgenic mice such as the $APP_{Swe}/PS1\Delta E9$ transgenic mice (APPxPS1) [7–11] accelerates the rate of amyloid brain pathology compared to mouse models targeting only one risk gene for AD [12].

We recently determined new behavioural characteristics of male APPxPS1 transgenic mice including impaired social recognition memory, task-dependent hyperlocomotion and anxiety, but no disruptions to sensorimotor gating [13]. Importantly, female APPxPS1 mice have previously been found to exhibit more extensive amyloid pathology compared to male transgenic mice [9] and increased Aβ accumulation has been shown to be correlated with deficits in spatial memory [14]. Female mice also develop cognitive impairments but the nature of those deficits reported varies across studies. For example, some studies detected learning deficits in the Morris water maze (MWM) at 8 and 10 months of age [15,16] whereas others described memory retention deficits at the age of 10 and 12 months [17,18] or no impaired memory retention at all [19]. Mice are not natural swimmers and inconsistencies in cognitive deficits of transgenic mice across studies could, for example, be due to differential levels of stress induced by variations in MWM protocols [20]. This would be in line with the observation that APPxPS1 females appear less anxious than control mice in some but not other laboratories [21,22].

An alternative to the MWM is the cheeseboard task (CB), which has been proposed to be a less stressful variant of the MWM as it focuses on positive reinforcement [23]. This is important when the mouse model in question exhibits an anxiety-related phenotype. The CB also avoids some of the issues surrounding MWM testing (e.g. floating behaviour, hypothermia, thigmotaxis and physical fatigue) [23–28]. Importantly, we have recently established the CB to reliably detect cognitive deficits [29,30]. Thus, in the current study, we aimed to further characterise female APPxPS1 double transgenic mice in novel behavioural paradigms with relevance to AD. We employed the CB as a novel test for spatial memory assessment and determined social behaviours in APPxPS1 females for the first time. We also analysed social and object recognition memory, fear-associated memory, sensorimotor gating as well as anxiety behaviour in these mice. Female APPxPS1 mice were tested at an age, where previous studies had reported relevant behavioural deficits and AD-relevant brain pathology [9,14,21,22,31].

2. Materials and methods

2.1. Animals

Double transgenic mice expressing chimeric mouse/human *APP* (Mo/HuAPP695swe/Swedish mutations K595N/M596L) and mutant human *PS1* (PS1/ΔE9) mice (APPxPS1) were obtained from Jackson Laboratory (Bar Harbour, USA; stock no. 004462, line 85) and maintained as double hemizygotes on C57BL/6JxC3H/HeJ background as described previously [7,8,12,32]. Female transgenic mice (APPxPS1; $N = 9$) and their non-transgenic littermates (WT; $N = 12$) were bred and group-housed in independently ventilated cages (Type Mouse Version 1: Airlaw, Smithfield, Australia) at Animal BioResources (Moss Vale, Australia). Test mice were transported to Neuroscience Research Australia (NeuRA) at around 10 weeks of age, where they were group-housed in Polysulfone cages (1144B: Techniplast, Rydalmere, Australia) with corn cob bedding (Pura Cob Premium: Able Scientific, Perth, Australia) and some tissues for nesting. Mice were kept under a 12:12 h light:dark schedule [light phase: white light (illumination: 124 lx)–dark phase: red light (illumination: <2 lx)]. Environmental temperature was automatically regulated at 21 ± 1 °C and relative humidity was 40–60%. Food (Rat and Mouse Maintenance Pellets: Gordon's Specialty Stockfeeds, Yanderra, Australia) and water were provided ad libitum, except where specified. Adult, female A/JArc mice from the Animal Resources Centre (Canning Vale, Australia) were used as standard opponents in the social preference test. Research and animal care procedures were approved by the University of New South Wales Animal Care and Ethics Committee in accordance with the Australian Code of Practice for the Care and Use of Animals for Scientific Purposes.

Table 1
Test age (weeks) and test biography of wild type-like control (WT) and double transgenic $APP_{Swe}/PS1\Delta E9$ (APPxPS1) female mice are shown.

Test age	Behavioural paradigm
30 ± 1	Light–dark test (LD)
30 ± 1	Elevated plus maze (EPM)
30 ± 1	Novel object recognition task (NORT)
31 ± 1	Social preference test (SPT)
34 ± 1	Contextual and cued fear conditioning (FC)
36 ± 1	Cheeseboard (CB)
38 ± 1	Reversal cheeseboard (rCB)
46 ± 1	Sensorimotor gating (prepulse inhibition: PPI)

2.2. Behavioural phenotyping

Starting at 7 months of age, mice were tested in a number of behavioural tests (Table 1) with an inter-test interval of at least 48 h as described earlier [13]. All tests were conducted during the first 5 h of the light phase to minimise effects of the circadian rhythm on the performance of test mice [33].

2.2.1. Light–dark test (LD)

The apparatus was an infrared photobeam-controlled open-field activity test chamber (MED Associates Inc., St Albans, USA) containing a dark box insert that covered half the chamber and was opaque to visible light. Light (illumination: 20 lx) and dark (illumination: <2 lx) compartments were connected by an opening located at the centre of the partition (for details see Ref. [34]). Mice were placed at the opening (faced towards the dark compartment) at the start of the experiment. The time spent and distance travelled in the two chambers were recorded for 10 min. Time spent as well as distance ratio (distance travelled in light chamber/total distance travelled) in the more aversive light chamber were selected as anxiety parameters.

2.2.2. Elevated plus maze (EPM)

The EPM assesses the natural conflict between the tendency of mice to explore a novel environment and avoidance of a brightly lit, elevated and open area [35,36]. The '+' apparatus consisted of two alternate open arms (illumination: 70 lx) and two alternate enclosed arms (illumination: 10 lx) connected by a central platform, and was elevated 70 cm above the floor. Mice were placed at the centre of the '+' of the grey PVC plus maze (for further details of apparatus see [37]) facing towards an enclosed arm and were allowed to explore the maze for 5 min. The time spent and distance travelled in the open and enclosed arms were recorded using AnyMaze™ (Stoelting, Wood Dale, USA) tracking software.

2.2.3. Novel object recognition task (NORT)

Object recognition memory in the NORT is demonstrated by the animal's ability to distinguish between familiar and unfamiliar objects (rodents have an innate preference towards novelty [38]). The NORT was conducted over 3 days (as described previously [39]): two trials (10 min per trial) were conducted per day with a 1 h intertrial interval (ITI). On day 1, mice were habituated to the empty arena during both trials. On day 2, mice were habituated

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