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Research report

# Ethological analysis of the senescence-accelerated P/8 mouse

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**Abstract**

Behaviour of senescence-accelerated (P/8) and resistant (R/1) mice was assessed using an ethological approach in a longitudinal study for exploratory and anxiety related behaviours (home cage activity, open field, elevated plus-maze and new object tests), cognitive abilities (step-down and step-through passive avoidance and water maze tests) and visual acuity (visible cliff test). Overall, P/8 mice showed higher activity induced by new environmental stimuli, higher anxiety and lower novelty seeking behaviour in the new object test than R/1 mice. P/8 mice showed an impaired performance as compared to R/1 mice in two passive avoidance tasks. Behavioural alterations of P/8 mice were already apparent at the age of 10–12 weeks. Factor analyses indicated that the impairment of P/8 mice in passive avoidance tasks relates to their altered exploratory and anxiety-related behaviour rather than to cognitive impairments. In the water maze, both strains performed badly in the visible platform task, suggesting poor visual abilities in both strains as supported by the visible cliff test. We conclude that, for a better interpretation of cognitive abilities of P/8 mice, tests not based on novelty-induced behaviour, visual acuity and good motor skills should be used. Finally, we question whether P/8 mice could be a model of some forms of neuropsychiatric disorders resulting from developmental abnormalities rather than ageing.


*Keywords:* Anxiety; Behaviour; Ethology; Factor analysis; Learning; Memory; Mouse; Passive Avoidance; P/8; R/1; SAM

## 1. Introduction

The senescence-accelerated mice (SAM) have been widely used as murine model of accelerated ageing. These mice were derived from an AKR/J colony following the observation that some offspring showed an inherited severe degree of advance of senescence [31]. Senescence prone (P) and senescence resistant (R) strains were then created by selective inbreeding. There are nine substrains of SAMP mice and three substrains of SAMR mice.

One of the SAMP substrains (P/8) has been suggested to be a model of age-related behavioural alteration, in particular with regard to cognitive-related behaviour [22,23], as well as a model for Alzheimer disease [11]. The R/1 strain has been commonly used as a control strain for the P/8 strain. P/8 mice showed an altered behaviour as compared to R/1 mice in several cognitive tests such as passive avoidance and one- and two-way active avoidance and T-maze active avoidance [8,9,14,23,24]. Less consistent results were obtained in spatial-related tasks, such as the water maze, the radial maze and the multiple T-maze [14,18,29]. P/8 mice also showed increased locomotion and exploratory behaviour in the open field and a lower anxiety profile in the elevated plus-maze and in the test for food neophobia as compared to the R/1 mice [21]. While some reports described behavioural alterations of P/8 mice already at an age of 2–4 months [18,21] most studies reported a clear difference between R/1 mice and P/8 mice starting only at the age of 8 or 12 months [10,11,14,20,29,32].

The previously observed age-dependent increase in locomotion can be problematic for the interpretation of the impaired performance of P/8 mice in cognitive tests such as the passive avoidance tasks where hyperactivity can lead to bad performances independently of cognitive abilities. Sim-

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ilarly, anxiety may account for an altered performance in cognitive tasks requiring aversive and stressful stimuli. Since the behaviour of a mouse in the open field and the elevated plus-maze depends on different components such as locomotor activity, exploratory drive, novelty-induced behaviour and anxiety, a clear interpretation of the results obtained in these tests is difficult unless a detailed analysis from an ethological perspective is performed.

With the aim to better elucidate the behavioural alterations of P/8 mice and whether their altered novelty-induced behaviour could account for their impaired performance in tasks for cognitive abilities, we investigated the exploratory and anxiety-related behaviour of P/8 mice and R/1 mice as well as their cognitive abilities in two passive avoidance tasks. Moreover, since inconsistent data have been obtained in spatial learning tasks, suggesting a general impairment of the P/8 and R/1 strains in these paradigms, we tested their performance in the water maze test.

## 2. Materials and methods

### 2.1. Animals and husbandry

P/8 and R/1 mice were bred under specific pathogen-free conditions. Food and water were supplied ad libitum. At the age of 8 weeks male mice were taken into a different animal facility and single-housed in 22 cm × 16 cm × 14 cm cages and maintained in a reversed 12 h light/dark cycle (light off at 7:00) under constant conditions (21 ± 1 °C; 60% humidity) for at least 2 weeks before being tested. The experimental room was adjacent to the animal facility and illuminated with red light. The equipment for experiments was cleaned after each mouse was tested by wiping with water and 70% ethanol. The open field test, elevated plus-maze test, new cage/new object test, home cage spontaneous behaviour, passive/active avoidance task, water maze task and visible cliff test were performed on 12 P/8 male mice and 12 R/1 male mice at the age of 10–12 weeks (but mice were 6 months old when tested in the water maze task). An additional open field experiment was performed on 17 P/8 mice and 12 R/1 mice at the age of 3 months and 12 P/8 mice at the age of 6 months. Two days after the open field these mice were tested in the visible cliff test and, after 1 week, in the step-down avoidance test. All experiments took place during the dark phase of the mice between 10:00 and 16:00 with at least 2-days break between different tests. All tests were recorded by video camera and evaluated by a trained experimenter blind to the strain of the mice.

### 2.2. Open field

The open field was an enclosed arena (50 cm × 50 cm × 40 cm) made of wood laminated with light-grey resin and illuminated with white light (lux = 25). The individual mice were gently placed into an opaque Plexiglas cylinder (Ø 11 cm × 23 cm) in the centre of the arena. The cylinder was remove after 30 s and mice could freely moved in the arena for 20 min. Total distance moved, mean velocity, mean distance to the wall (a parameter for thigmotaxis) and time spent in the centre (an imaginary inner square of 20 cm × 20 cm) were analysed with the software EthoVision (Noldus, Wageningen, The Netherlands). A trained observer using the software The Observer (Noldus) scored the behaviour of the animals during the first 5 min of the test. The following behavioural parameters were analysed: risk assessment (the mouse stretches forward and retracted to the original position without forward locomotion), sniffing (rapid movement of the nostrils towards the surface of the open field), rearing off wall (vertical exploration by standing on the hindpaws), rearing on wall (vertical exploration by standing on the hind limbs with one or two front paws at the wall), jumping and self-grooming.

### 2.3. Elevated plus-maze

The elevated plus-maze had the shape of a plus elevated 75 cm above the ground and consisted of two opposite open arms and two closed arms (each 30 cm × 5 cm) extending from a central platform (5 cm × 5 cm). Closed arms were surrounded by walls (15 cm). The maze was made of white PVC and illuminated with white light (lux = 20). Mice were gently placed into the centre facing an open arm and exploration of the maze was video-recorded for 5 min. The number of entries with all the four paws into the arms or centre, time spent on the arms or centre, protected exploration of the open arms (the mouse, keeping the hind limbs in the closed arms or centre moves its head over the sides of the open arm) and unprotected exploration of the open arms (mouse enters with four front paws an open arm and the head moves over the sides of the open arm) were scored with the software The Observer.

### 2.4. New cage/new object

Mice were placed into a new and larger cage (38 cm × 22 cm × 15 cm) with fresh bedding and video-recorded for 5 min. They were then left undisturbed in the new cage. After 24 h the behaviour in the new cage (now familiar to the mouse) was video-recorded for 5 min before introducing a new object into the cage. The new object consisted of a water bottle (7 cm × 7 cm × 10 cm) for rodents with the bottom cut off and with a hole of 3 cm × 4 cm on one side. The new object was placed into one side of the cage standing upright with the metallic top fixed between the bars of the cage top and the hole facing the centre of the cage. Behaviour was video-recorded for 5 min after the new object was introduced into the cage. The following behavioural parameters were analysed using the software The Observer: sniffing and self-grooming, rearing (definition as in open field, but without differentiation between on wall and off wall), digging (rapid movement of the front paws in the bedding), climbing (three or four paws on the grid at the top of the cage) and eating/drinking (chew-