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Assessment of social interaction and anxiety-like behavior in senescence-accelerated-prone and -resistant mice

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HIGHLIGHTS

- SAMP and SAMR1 mice were tested in social approach and object recognition tests.
- SAMP mice showed evidence of greater anxiety-like behavior than SAMR1 mice.
- Reduced sociability was seen in SAMP mice compared to SAMR1 mice.
- SAMP mice spent more time in protected areas and less in exposed areas than SAMR1 mice.

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ABSTRACT

Two members of the senescence-accelerated mouse group, SAMP8 and SAMP10, are characterized by learning and memory deficits, while the SAMR1 strain is not. In this study, we used two behavioral tests, social approach and object recognition and compared the results observed for the SAMP strains with those seen in the control strain, SAMR1. In social approach experiments, the 2 SAMP strains showed decreased sociability compared to SAMR1 as shown by their reluctance to spend time near a stranger mouse and increased immobility. In object recognition experiments, SAMP strains spent more time in the thigmotaxis zone and less time in the more exposed central zone than SAMR1 mice. From a behavioral standpoint, SAMP mice were less interactive and showed increased anxiety-like behavior compared to SAMR1.

1. Introduction

The factors that influence social behavior of mice are largely unknown. The opportunity to examine strains of mice from similar genetic backgrounds that nevertheless contain differences is provided by the senescence accelerated mouse (SAM) system [1]. The 2 distinct strain groups are senescence-prone (SAMP) and senescence-resistant (SAMR). All of these strains originated in a cross between the AKR strain and one or more unknown strains. Subsequent deliberate inbreeding of the original prodigy led to a series of 9 SAMP strains and 5 SAMR strains. All of the SAMP strains shared a number of characteristics that differed from those of SAMR1: a shorter life span, ruffled and/or dull coat, abnormal curvature of the spine and periorbital inflammation. There are also problematic characteristics that are found only in a single or in several SAMP strains: cataract, in SAMP9; senile osteoporosis, in SAMP6; senile amyloidosis, in SAMP strains 1, 2, 7 and 11; and deficits in learning and memory, in SAMP8 and SAMP10 [1]. Learning and memory deficits in SAMP8 and SAMP10 have been analyzed extensively using a variety of tests: passive avoidance, active avoidance, and water maze [2–6]. Results from these and other tests established that learning and memory deficits are characteristic of SAMP8 and SAMP10 strains.

Another component of overall behavior in rodents involves the tendency for social interaction which may, in part, be based on the animal's level of anxiety. Several studies have examined the relationship between aging, anxiety and social interaction. Studies have shown increased anxiety-like behavior in aged mice [7] and rats [8,9] as measured by the elevated plus maze. Decreased social interaction has also been reported in aged rats [10,11], although the contribution of anxiety to these results was questioned by the authors. Previous studies of aging and anxiety using the SAM model have indicated reduced [12–14] or little difference [15] in anxiety in SAMP vs. SAMR1 strains. Social interaction with regard to anxiety in SAM has not been reported.

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To further explore the relationship between aging, anxiety and social interaction in the SAM model, age-matched SAMR1, SAMP8 and SAMP10 were tested using two behavior tests: social approach [16,17] and object recognition [18]. The social approach test utilizes a three-chambered box to determine if a test mouse would rather spend time with an unfamiliar (stranger) mouse or with an unfamiliar inanimate object (novel object). The object recognition test measures preference for novelty by use of unfamiliar objects in an open field. The object recognition test can also be used to measure anxiety by recording the amount of time spent near the walls of the apparatus (thigmotaxis zone) versus the more exposed central area (central zone). The results indicate that SAMP8 and SAMP10 have reduced levels of social interaction compared to SAMR1 and that the level of anxiety is higher in SAMP strains than in SAMR1.

2. Material and methods

2.1. Mice

SAMR1, SAMP8 and SAMP10 strains were kindly provided by Dr. Toshio Takeda (Kyoto University, Kyoto, Japan) and have been maintained in our animal colony for the past 17 years. Mice were maintained in accordance with the Guide for the Care and Use of Laboratory Animals. Mice were maintained in a temperature- and humidity-controlled environment, with a 12-h light–dark cycle (lights on from 6 a.m. to 6 p.m.), and all experiments were done during the 6 a.m.–6 p.m. time period. Mice were given food and water ad libitum. All experiments were conducted using female mice. Social approach was done using mice from 5 months to 15 months of age. Object recognition was done using mice from 5 to 14 months of age. Experiments were approved by the Institute for Basic Research Institutional Animal Care and Use Committee.

2.1.1. Social approach test

SAM were evaluated for willingness to approach and interact with an unfamiliar mouse using a three-chambered test box [16,17] and tracking software (ANY-maze, version 4.75). The test mouse is placed in the center chamber of the test apparatus for a five-minute acclimatization period. Subsequently, gates are raised that allowed the mouse to explore chambers on either side of the center chamber (habituation trial) for a 10-min period. The mouse is then returned to the center chamber and the gates are closed. A small wire cage containing an unfamiliar mouse (stranger) is placed in one of the side chambers (stranger chamber) and an identical empty wire cage is placed in the other side chamber (novel object chamber). The stranger chamber is alternated between the left and right sides to prevent bias. The center chamber gates are then opened, allowing the test mouse access to both the stranger chamber and novel object chamber for 10 min (sociability trial). The small wire cage holds the stranger mouse in a specific area, but allows the test mouse to interact socially with the stranger.

During the habituation and sociability trials, the test mouse's movements are tracked with an overhead camera. The tracking software can also distinguish the nose and body of the mouse. The stranger mouse cage and novel object cage are placed within small predefined areas of the stranger and novel object chambers. These areas constitute the sniff zone. When the nose of the mouse enters these areas, this is measured as time in the novel object or stranger sniff zone.

2.1.2. Object recognition

We used the object recognition procedure described by Hammond et al. [18] with several modifications. Mice were placed in a 38 cm-square arena. Movement was recorded with a video camera 150 cm above the arena floor which was interfaced with the ANY-maze 4.6 video tracking system. The parameters established for the analysis were as follows: thigmotaxis zone, 7.62 cm from wall; object zones, 8.9 cm square; and central zone, 22.9 cm square.

Mice were placed in the testing room at least 30 min prior to the start of the test. The acclimatization was the same prior to each session. Mice were then tested in 4 sessions of 5 min each session on 2 consecutive days, one session in the morning, and one session in the afternoon. The parameters for the sessions were as follows: session 1, the arena was empty; sessions 2 and 3, identical objects in the SW and NE object zones; and session 4, the same familiar object in SW zone and a novel object in the NE zone. Time spent in the thigmotaxis zone and in the central zone was recorded.

3. Results

3.1. Social approach

SAMP8 and SAMP10 strains exhibited increased reluctance to approach a stranger mouse compared to SAMR1.

SAMP8 and SAMP10 both spent more time immobile than SAMR1 during the social approach test (Fig. 1). Increased immobility was particularly apparent in older SAMP10, measured at 8–12 months and 15 months (Fig. 1).

SAMP8 and SAMP10 were more reluctant than SAMR1 to spend time in the chamber containing an unfamiliar mouse (Fig. 2). SAMP8 and SAMP10 also spent less time than SAMR1 in close interaction (the sniff zone) with the stranger mouse (Fig. 3). This decrease in time spent by SAMP8 and SAMP10 in approach and interaction was seen in all the age groups tested.

The 8–12 month SAMP10 group spent significantly more time in the center zone than SAMR1 (136.1 s ± 13.9 vs. 75.0 s ± 6.7, respectively, $p = 0.0002$). This difference may be reflected in the significantly greater time immobile exhibited by this group (Fig. 1). The 5- to 8-month-old SAMP8 and the 5-month-old SAMP10 spent significantly more time in the novel object chamber than their SAMR1 counterparts (176.9 s ± 13.6 vs. 135.8 s ± 9.7, $p = 0.02$ and 162.0 s ± 15.2 vs. 114.8 s ± 12.5, $p = 0.03$, respectively). There were no significant differences in time spent in the novel object sniff zone between SAMR1 and SAMP8 or SAMP10 at any age group.

3.2. Modified object recognition

In the modified object recognition test described in the Material and methods section, there were no differences among the strains with regard to increased attention to the novel object, which was placed in the arena in Session 4. There did appear to be strain differences in the response of mice to the enlarged accessible area, termed the arena. Chief among these was the difference between the two

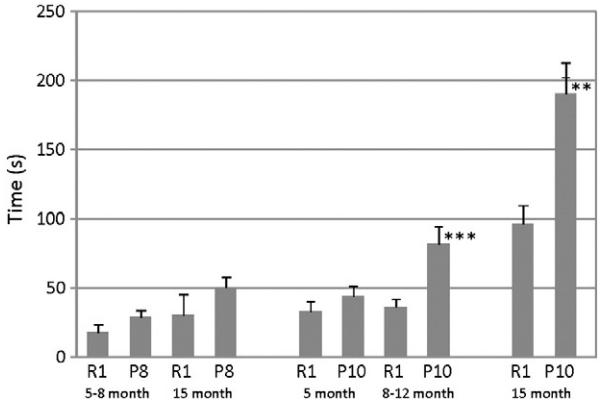

Fig. 1. Total time immobile in social approach test. Five to eight month R1 vs. P8: n = 20 R1, 20 P8. Fifteen month R1 vs. P8: n = 7 R1, 7 P8. Five month R1 vs. P10: n = 10 R1, 9 P10. Eight to twelve month R1 vs. P10: n = 40 R1, 41 P10. Fifteen month R1 vs. P10: n = 11 R1, 11 P10. *** – $p < 0.001$, and ** – $p < 0.01$, R1 vs. P10.