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Spatial delayed nonmatching-to-sample performances in long-living Ames dwarf mice

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Abstract

Ames dwarf mice have an extended lifespan by comparison with normal mice. Behavioral testing has revealed that sometimes Ames dwarf mice also evince superior performances relative to normal mice, but in other cases they do not. In this experiment, Ames dwarf and normal mice were compared on a T-maze test and on a delayed nonmatching-to-sample variant of a T-maze test. On the simple T-maze, Ames dwarf and normal mice committed comparable numbers of errors. On the nonmatching-to-sample task, normal mice mastered the discrimination by the end of the experiment while Ames dwarf mice did not. The apparatus, distances traveled and session duration were equivalent between the two tasks. The poorer performances of Ames dwarf mice on the nonmatching-to-sample task suggests that Ames dwarf mice may not be as capable of learning relatively cognitively complex tasks as normal mice.

Keywords

Ames dwarf mouse; Aging; Longevity; Learning; Reinforcement

1. Introduction

Ames dwarf mice homozygously express a Prop-1 point mutation on Chromosome 11, which impairs anterior pituitary development and results in a deficiency of peripheral growth hormone (GH), prolactin, and thyroid-stimulating hormone, and secondary deficiencies in circulating insulin growth factor-1 (IGF-1), insulin, and the insulin-IGF-1 signaling cascade [1–4]. These endocrine-mutant mice also show reduced sexual dimorphism [5], and they reach only one-third of the size of wild type siblings [6]. However, Ames dwarf mice live significantly longer than their wild type siblings (49% longer among males, 68% longer among females) and thereby provide a naturally occurring model of delayed aging [7].

The discovery that Ames dwarf mice live approximately 50% longer than wild type mice has led researchers to examine physiological differences between Ames dwarf and wild type mice. Research of this kind has shown that Ames dwarf mice have greater resistance, in vitro and in vivo, to oxidative stress and to neurotoxins [8–15]. Ames dwarf mice have also been

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found to generate IGF-I independent of the hypothalamic-pituitary axis and to have elevated rates of neurogenesis in the hippocampus relative to wild type mice [16–19].

This pattern of longer life, greater resistance to neuronal damage, and elevated neurogenesis suggests that Ames dwarf mice will also show improvements, relative to wild type mice, on measures of learning and behavior. Positive indications that this is indeed the case have been obtained [20–23], but only tentative conclusions can be reached at this time. Only a few studies to date have examined the behavior of Ames dwarf mice and these have examined only certain facets of learning. Furthermore, the results of these studies have been somewhat mixed. Ames dwarf mice have been found to do at least as well as wild type mice on measures of inhibitory avoidance and/or spatial learning [21–23], but not on two traditional measures of operant behavior (specifically, a matching-to-sample task and a fixed-interval schedule of reinforcement) [24].

The relatively good performances of Ames dwarf mice on some measures of learning, but not on others, hint at a differential effect of the Prop-1 mutation. Perhaps Ames dwarf mice fare well on tasks closely related to basic survival (the spatial learning and inhibitory avoidance tasks serve as analogs of exploration, foraging, and predator avoidance), but not on tasks involving other types of learning processes (e.g., efficient performances on fixed-interval schedules require subjects to accurately gauge the passage of time).

However, comparisons between Ames dwarf and wild type mice are also complicated by nonlearning factors that may differentially affect the performances of Ames dwarf mice. For example, Ames dwarf mice, because of their smaller size, might more easily become fatigued or satiated than wild type mice. The traditional operant learning tasks used by Derenne et al. [24] were designed to mitigate the potential influence of fatigue and satiation. The response required little movement, the reinforcer was provided in small amounts, and sessions ended after only a few reinforcers were delivered. However, other motivation-liked differences may not be so easy to control.

An informal observation within our lab is that the Ames dwarf mice spend most of their time huddled together (several mice share a single home cage) and that they are noticeably less active than wild type mice. Possibly this is related to the finding that Ames dwarf mice have a lower internal body temperature (1.5 °C lower) than wild type mice [25]. Observations by others suggest that a relative lack of activity is broadly characteristic of Ames dwarf mice and phenotypically identical Snell dwarf mice (the latter have a Pit-1 mutation and anterior pituitary hypoplasia) [20,21,26–31]. Perhaps this relative “activity deficit”, regardless of cause, prevents dwarf mice from responding in a prompt and efficient manner on free operant learning tasks.

The following experiment was designed to disentangle the behavioral contributions of learning and nonlearning factors on the performances of Ames dwarf and wild type mice. We first sought to replicate the finding, reported by Sharma et al. [23], that older Ames dwarf mice perform as well as age-matched wild type mice on a T-maze test. Afterwards, we observed the same subjects on a nonmatching-to-sample variant of the T-maze test. The second task required subjects to travel the same distances within the same timeframe as was

used with the former task. The difference in the tasks concerned how subjects were able to obtain reinforcement. On the simple T-maze task, the reinforcer was always located in the same goal arm. On the nonmatching-to-sample task, the location of the reinforcer varied. More specifically, on odd-numbered trials, subjects were forced to enter one goal arm to find the reinforcer, while on even-numbered trials subjects could enter either goal arm, but the reinforcer was available only in the arm opposite to that used on forced-choice trials. In other words, the second test was designed to be more cognitively complex than the simple T-maze test, but no more physically demanding.

A secondary comparison concerned the effects of two different reinforcers on performances. Half of the subjects trained with the simple T-maze procedure were given a saccharin solution as a reinforcer (in line with the experiment by Derenne et al. [24]) and the other half were given a diluted sweetened condensed milk reinforce (in line with the experiment by Sharma et al. [23]). The more efficacious of the two reinforcers was used for all subjects on the nonmatching-to-sample task.

2. Methods

2.1. Subjects

Subjects were 19 Ames dwarf mice and 15 wild type mice, bred and maintained at the University of North Dakota (UND) Center for Biomedical Research facilities under controlled conditions of photo-period (12 h light/12 h dark) and temperature (22 ± 1 °C). The Ames dwarf (*df/df*) mice used in this study were derived from a closed colony with heterogeneous background (over 30 years). Dwarf mice were generated by mating either homozygous (*df/df*) or heterozygous (*df/+*) dwarf males with carrier females (*df/+*). Subjects were about 20 months old at the time of data collection; for reference, the average lifespan of the wild-type mice in our colony is 23–24 months (Brown-Borg et al. 1996). The increase in average life span exceeds 350 days for males and 450 days for females.

Data collection occurred 3 hours after the light cycle commenced, for 5 days a week. Thirty minutes after data collection ended, the mice were given free access to food (Harlan Teklad, Wilmington, DE, USA; Lab-diet 8640) and water for 3 hours in their home cages. Afterwards, the food and water were removed. Weights (recorded daily) remained stable throughout the period of observation.

2.2. Simple T-maze procedure

Subjects were observed in an opaque T-maze designed for mice (SD Instruments, Inc.) following the procedure adopted by Sharma et al. [23]. On Day 1, a small cup filled with the reinforcer was placed at the end of each goal arm and subjects were allowed to freely explore the maze for 10 min. For ten of the Ames dwarf mice and seven of the wild type mice, the reinforcer consisted of diluted (1:1 with tap water) sweetened condensed milk. For the remaining nine Ames dwarf mice and eight wild type mice, the reinforcer consisted of a 0.2% saccharin solution. These reinforcer assignments remained in effect during the subsequent training and probe sessions.

Subjects received training sessions on Days 2 through 4. Each training session consisted of four trials. On each trial, 50 μ l of the reinforcer was placed in a cup at the end of one goal arm. The other cup remained empty. Subjects were trained against their preference during these sessions, that is, the reinforcer consistently was placed in the goal arm that the subject had visited less often on Day 1.

Two probe sessions were conducted on Day 5 and Day 12 to help shed light on the type of learning that had occurred during training. Both sessions consisted of two trials on which the maze was rotated 180° from the orientation used during training sessions. The reinforcer was placed in the opposite goal arm than had been used during training; all other cues, including the experimenter, remained stationary. Subjects could find the reinforcer by moving in the same spatial direction that they had on training trials (e.g., by turning towards the north), but not by making the same turn that they had on training trials (e.g., by turning right). The former response suggested that subjects used a “place strategy” to locate the reinforcer, while the latter response suggested that subjects instead used a “response strategy” [23,32,33].

During training sessions, trials ended after subjects obtained reinforcement; an initial visit to the goal arm without the reinforcer was counted as an error. During the Day 5 and Day 12 probe sessions, the subject was allowed to enter only a single arm. On all days, the T-maze was swabbed with 70% ethanol between subjects to eliminate odors.

2.3. Nonmatching-to-sample procedure

After completion of the simple T-maze procedure, subjects were observed under a nonmatching-to-sample variant of this procedure. Subjects received a total of 12 nonmatching-to-sample sessions, and each session consisted of four trials. On every trial the reinforcer (for all subjects this was 50 μ l of diluted sweetened condensed milk) was placed in a cup at the end of one goal arm. The other cup remained empty. Trials 1 and 3 of each session were “sample” trials; on these trials subjects had access to the goal arm which contained the reinforcer and the other goal arm was closed off. The goal arm that held the reinforcer differed across subjects. In every case, however, the arm selected to hold the reinforcer was the same arm that subjects had been trained to approach under the simple T-maze procedure. Trials 2 and 4 were “test” trials; on these trials subjects had access to both goal arms, and the reinforcer was placed in the arm that had been previously inaccessible. Data analysis was based solely on performances during the test trials. An initial visit to the arm without the reinforcer was counted as an error.

3. Results

3.1. Simple T-maze results

Statistical comparisons were made mixed-model ANOVAs, in which performances were compared across mouse and reinforcer type, and within either the three acquisition sessions or the two probe trial sessions. The analysis was conducted on three aspects of performances: the mean number of trials completed by each subject, the mean duration of each trial, and the mean number of errors emitted on each trial.

Training trials were more frequently completed when condensed milk was provided (mean and standard error of the mean = $99.0 \pm .04\%$) than when the saccharin solution was provided ($M = 83.5 \pm .04\%$), $F(1, 30) = 6.78$, $p = .014$. Trial completion did not depend on the type of mouse ($p = .357$), and did not vary across the three training sessions ($p = .163$). The interactions were similarly nonsignificant.

Differences in the mean duration of each trial between Ames dwarf and wild type mice (Fig. 1, top row) did not reach the level of statistical significance ($M = 28.90 \pm 5.11$ s for Ames dwarf mice, $M = 33.77 \pm 5.76$ s for wild type mice; $p = .532$). Trial durations varied across the three days, $F(2, 60) = 6.52$, $p = .003$. Tukey's LSD test of pairwise comparisons revealed that trial durations on Day 2 ($M = 37.93 \pm 5.33$ s) and Day 3 ($M = 32.32 \pm 4.37$ s) were significantly longer than those on Day 4 ($M = 23.76 \pm 3.54$ s). The interaction of mouse type and day was nonsignificant ($p = .847$).

Subjects completed training trials more quickly when diluted condensed milk was provided ($M = 15.47 \pm 5.48$ s) than when a saccharin solution was provided ($M = 47.20 \pm 5.40$ s), $F(1, 30) = 17.00$, $p < .001$. The interaction between the day of observation and the type of reinforcer was nonsignificant ($p = .809$) as was the interaction between the day of observation, the type of reinforcer, and the type of mouse ($p = .284$).

Differences in the number of errors in each trial between Ames dwarf and wild type mice (Fig. 1, bottom row) did not reach the level of statistical significance ($M = 1.28 \pm .17$ errors per trial for Ames dwarf mice, $M = 1.72 \pm .19$ errors for wild type mice; $p = .092$). Mean errors varied across the three days, $F(2, 60) = 7.08$, $p = .002$. Tukey's LSD test of pairwise comparisons revealed that subjects committed more errors on Day 2 ($M = 1.84 \pm .23$) and Day 3 ($M = 1.72 \pm .23$) than on Day 4 ($M = .92 \pm .13$). The interaction of mouse type and day was nonsignificant ($p = .309$).

Subjects committed fewer errors when diluted condensed milk was provided ($M = .86 \pm .18$ errors per trial) than when a saccharin solution was provided ($M = 2.13 \pm .18$), $F(1, 30) = 24.69$, $p < .001$. The interaction between the day of observation and the type of reinforcer was nonsignificant ($p = .341$) as was the interaction between the day of observation, the type of reinforcer, and the type of mouse ($p = .327$).

As for performances during the probe trials (Day 5 and Day 12), all subjects completed all trials. Differences in trial duration did not reach the level of statistical significance as a function of mouse type ($p = .091$) or reinforcer type ($p = .304$). The interaction was likewise nonsignificant ($p = .193$). Ames dwarf mice used what can be termed a spatial strategy and a response strategy with equal frequency ($50 \pm 28\%$). The responses of wild type mice were consistent with a response strategy $68 \pm 15\%$ of the time, but this difference with respect to dwarf mice fell short of statistical significance ($p = .079$). Differences due to reinforcer type ($p = .754$) and the interaction ($p = .730$) were also nonsignificant.

3.2. Nonmatching-to-sample results

Statistical analysis of performances consisted of mixed-model ANOVAs that compared performances of the two types of mice at two different points in the experiment. The

nonmatching-to-sample procedure included three times as many training trials as the simple *T*-test in anticipation of the finding that subjects would be slower to show improvements in performance on the former task. To simplify the analysis of practice effects, an a priori decision was made to compare performances during the first three sessions with those during the last three sessions (the same mode of analysis reported by Derenne et al.). This statistical analysis was performed once with mean trial durations and once with mean errors per trial (subjects completed 98% of trials, and these data were not submitted to statistical analysis).

Differences in the mean duration of each trial between Ames dwarf and wild type mice (Fig. 2, top row) did not reach the level of statistical significance ($M = 7.88 \pm 1.74$ s for Ames dwarf mice, $M = 8.30 \pm 1.95$ s for wild type mice; $p = .874$). Trial durations also did not significantly differ as a function of practice ($M = 7.75 \pm .96$ s for the early sessions, $M = 8.44 \pm 2.35$ s for the final sessions; $p = .780$). The interaction was likewise nonsignificant ($p = .480$).

As for the accuracy of responses (Fig. 2, bottom row), Ames dwarf mice committed more errors per trial ($M = .47 \pm .05$) than wild type mice ($M = .27 \pm .06$), $F(1, 32) = 7.19$, $p = .012$. Errors were also more frequent during the early sessions ($M = .47 \pm .05$) than during the final sessions ($M = .27 \pm .05$), $F(1, 32) = 8.26$, $p = .007$. Although Fig. 2 suggests that the largest difference in the mean number of errors per trial occurred during the final sessions, the interaction of mouse type and point within the experiment was nonsignificant ($p = .149$).

4. Discussion

Ames dwarf and wild type mice were compared on a simple T-maze task and on a nonmatching-to-sample variant of that task. The simple T-maze task partially replicates an experiment by Sharma et al. [23]. One notable difference was that Sharma et al. had groups of two different ages, both of which were considerably younger than those used in the present experiment. Within a group that was 3 months, Ames dwarf mice completed trials in less time and made fewer errors than wild type mice. Within the group that was 12 months, no difference was found in the performances of Ames dwarf and wild type mice. Our subjects were considerably older than those used by Sharma et al. (subjects were about 20 months old, or near the mean lifespan of wild type mice [7]). By finding no significant performance differences in subjects of this age, we confirmed and extended Sharma et al.'s findings with 12-month-old mice.

Another point of departure in methods concerned the comparison, reported here, of performances with two different reinforcers (saccharin solution vs. diluted condensed milk). Subjects completed more trials, completed trials in less time, and committed fewer errors when milk was used as a reinforcer than when saccharin was used. A notable finding is that Ames dwarf mice performed at least as well as wild type mice when saccharin was available, suggesting that differential motivation for this reinforcer per se does not explain the poorer performances of Ames dwarf mice in the operant learning experiment by Derenne et al. [24] in which saccharin was also used.

The most important findings concern the differences in performance between the simple T-maze test and the nonmatching-to-sample variant of this task. The nonmatching-to-sample task involved the same timeframe, distances, and number of trials as the simple T-maze task. The primary difference was that on nonmatching-to-sample task test trials, subjects were required to remember which choice they had made previously and then to select the opposite of that choice. In other words, the task was not more physically demanding than the simple T-maze task, but it was more cognitively demanding. This is an important point, as Ames dwarf mice are of smaller size than wild type mice, and possibly are more prone to satiation and fatigue than wild type mice. There are also indications that dwarf mice evince a kind of activity deficit [20,21,26–31] which could impinge on learning tasks requiring locomotor behavior. Establishing that these putative factors did not produce poorer performances on the simple T-maze task suggests that they were unlikely to have been a significant factor affecting performances on the nonmatching-to-sample variant of the T-maze task. In other words, the poorer performance of Ames dwarf mice on the nonmatching-to-sample task reported here appears to be a clear indication of some kind of learning deficit is present in Ames dwarf mice.

The present experiment does not fully reveal the scope of a learning deficit in Ames dwarf mice. It is possible, for example, that had the two groups of mice received additional training than Ames dwarf mice would have eventually learned to make as few errors as wild type mice. Conversely, it is also possible that additional training would have revealed sustained performance differences. It also remains to be determined whether a learning deficit in Ames dwarf mice is relatively widespread and important. Possibly, as suggested in Introduction, the deficit may be as broad as any behavioral task that involves skills not closely related to basic survival. However, it is also possible that the effects of such a learning deficit are considerably more limited and of less importance than the factors responsible for the superior performances in Ames dwarf mice in other circumstances. Ames dwarf mice have been found to evince changes within the hippocampus with potentially broad procognitive effects [16–18,34]. In any case, much has yet to be discovered about the learning and behavioral differences created by the Prop-1 mutation, the mechanisms within the brain responsible for these changes, and the bearing that such effects may have on efforts to use long-living Ames dwarf mice as a platform for discovering how to promote successful aging.

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HIGHLIGHTS

- Long-living Ames dwarf mice and normal mice were compared on a spatial delayed nonmatching-to-sample task.
- Ames dwarf mice made more errors than normal mice.
- The Prop-1 mutation in Ames dwarf mice has surprising and inconsistent effects on learning and memory.

Fig. 1.
Mean trial duration and mean errors per trial during T-maze training sessions. Vertical lines within the figure show the standard error of the mean.

Fig. 2.

Mean trial duration and mean errors per trial on the nonmatching-to-sample variant of the T-maze task. The 12 days of observation are identified as D1–D12. The lines above each bar show the standard error of the mean.