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Effects of pregnancy experience on ovarian senescence and longevity in Hatano rats bred for high- and low-avoidance learning

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ABSTRACT

We investigated the effects of pregnancy experience on ovarian senescence and longevity using two inbred strains of Hatano rats. These strains have been selectively bred for high- and low-avoidance animals (HAA and LAA, respectively), but the HAA line has a slower onset of ovarian senescence and a shorter lifespan compared with the LAA line. The onset of abnormal estrous cycles and survival curves were compared between nulliparous and parous rats in each line. In the HAA line, pregnancy experience did not change the onset of ovarian senescence but increased longevity. This suggests that a pituitary tumor, which is a causal factor for accelerated mortality in this line, developed slowly in parous rats. In the LAA line, pregnancy experience delayed the onset of ovarian senescence and reduced the incidence of mammary tumors but did not increase longevity because of an increased frequency of constipation with megacolon. These data suggest that the effects of pregnancy experience on ovarian senescence and longevity depend on the reproductive characteristics of the rat strains.

1. Introduction

Reproductive factors, such as age at menarche, parity, and age at menopause, influence the longevity of women in cohort studies (Wu et al., 2014; Levine et al., 2016; Sun et al., 2015). A comparative study between the number of children and telomere length in Mayan women reported that women who had fewer children had shorter telomere lengths than those who had more children (Barha et al., 2016). Telomeres may be protected from oxidative stress by estradiol, which increases during pregnancy, because estradiol is a potent antioxidant in cells (Barrett and Richardson, 2011; Behl et al., 1995). Nulliparous women have a higher risk of breast cancer compared with women who have undergone single or multiple pregnancies early in life (Kelsey, 1993; MacMahon et al., 1970). Short-term exposure of estradiol at pregnancy levels in rats suppresses chemically induced breast cancer (Guzman et al., 1999; Rajkumar et al., 2001). Parous women have lower prolactin levels than those in nulliparous women, which reduce the risk of developing breast cancer (Musey et al., 1987; Thordarson et al., 1995). However, in cohort studies, the relationship between reproductive factors and longevity is confounded by non-reproductive factors such as smoking habits, obesity, education levels, and nutrition status (Merritt et al., 2015). Therefore, it is important to develop animal models to analyze the relationship between reproductive factors and longevity.

We used two inbred strains of Hatano rats that have been genetically selected and bred from Sprague-Dawley rats on the basis of performance in shuttle-box tasks (Ohta et al., 1995). High-avoidance animals (HAA) are good at avoidance learning, and low-avoidance animals (LAA) are poor at avoidance learning. Avoidance learning is a process by which an animal learns a behavioral response to avoid aversive stimuli and is a likely dopaminergic mechanism (Ilango et al., 2012). Selective breeding has resulted in different release patterns of estrogen, progesterone, and prolactin during estrous cycles, and the interval is longer in LAA rats than in HAA rats (Asai et al., 2002). The two strains also have clear differences in puberty where the vaginal opening occurs at younger age in HAA rats (Shirota et al., 2004), and in reproductive senescence where abnormal estrous cycles occur at younger age in LAA rats (Ohta et al., 2016). Female HAA rats are more likely to develop pituitary tumors and female LAA rats are more likely to develop mammary tumors (Ohta et al., 2016). HAA rats have bigger adrenal glands and react more to stress than LAA rats (Ohta et al., 1999). For example, gastric erosion under restraint stress in water occurs at higher rate in HAA rats than in LAA rats (Asai et al., 2006). In addition, plasma ACTH levels under acute restraint stress are higher, but plasma prolactin levels are lower, in HAA rats than in LAA rats (Asai et al., 2004). These endocrinological differences between HAA and LAA rats probably result from differences in the hypothalamus-pituitary-adrenal axis (Akieda-Asai et al., 2011) and the hypothalamus-pituitary-gonadal axis

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(Jaroenporn et al., 2011).

In this study, we examined the effects of pregnancy experience on ovarian senescence and on longevity using HAA and LAA Hatano rats to analyze the relationship between reproductive factors and longevity.

2. Materials and methods

2.1. Animals and housing

HAA and LAA lines maintained by sib-mating for over 25 years at the Hatano Research Institute were used and are available from the National BioResource Project - Rat (http://www.anim.med.kyoto-u.ac.jp/NBR/). Representative samples of colonies were examined by microbiological monitoring test 3 times per year, and no significant titers were found. Females were kept individually in metal cages with a metal meshed floor (220w x 270d x 190 h mm) in an animal room maintained at a room temperature of 22–25 °C, a relative humidity of 50–65%, and 12-h lighting (lighting period: between 7:00 and 19:00). Feed (CE-2 pellet feed, CLEA Japan) and tap water were available *ad libitum*. Cages were changed and autoclaved weekly. Copulated females were housed individually in TPX synthetic resin cages (350w x 400d x 180 h mm) with Paper Clean (SLC Japan) from gestational day 18 through postpartum day 10. Immature females were housed 2 or 3 littermates per cage from weaning through 10 weeks of age. The general condition of all tested animals was observed once a day. Animal protocols were reviewed and approved by the Animal Care and Use Committee of the Food and Drug Safety Center (FDSC) in compliance with the Guideline for Animal Experiments at Hatano Research Institute, FDSC.

2.2. Ovarian senescence and survival rate

Ovarian senescence was examined by vaginal smears around 8 to 11 months of age because estrous cycles are easily disturbed between 6 and 12 months in Sprague-Dawley rats. Eight cohorts for each line were used. Vaginal smear age and pregnancy experience are shown in Table 1. Estrous cycles and lifespans of Cohorts A, B, and C were compared previously between HAA and LAA lines (Ohta et al., 2016). Vaginal smears were collected daily between 7:00 and 11:30. Smears stained with Giemsa were examined microscopically and were classified based on the cell types observed in the vaginal smears. Estrous cycles were categorized every 2-week observation period as a normal cycle (regular 4- or 5-day cycle) or an abnormal cycle, which included long cycles (cycles of 6 days or more), persistent estrus (a minimum of 3 consecutive days of estrus or pro-estrus), and constant diestrus (non-cycling and anestrus). Rodent estrous cycles typically change from normal cycles to long cycles to persistent estrus and lastly to anestrus (Finch et al., 1984). Because rodents lack a vaginal discharge equivalent to menstrual flow, ovarian senescence is not termed menopause (Finch, 2014).

To determine survival curves, females of Cohorts A, B, C, E, F, and G lived out their natural lifespans until 24 months of age as described previously (Ohta et al., 2016). Females still alive between 105 and 106 weeks of age were exsanguinated under sodium pentobarbital anesthesia and subjected to necropsy. Intermediate dead and moribund females were also subjected to necropsy.

To measure the weight of endocrine organs, females in Cohorts D and H were sacrificed at 52 weeks of age. These females were exsanguinated under sodium pentobarbital anesthesia, and the weights of the pituitary gland, adrenal gland, and ovary were measured.

Table 1
Vaginal smear age and pregnancy experience of Cohorts in the HAA and LAA lines.

Cohort	Number of females		Pregnancy experience	Age examined vaginal smear	Purpose	Terminal age
	HAA	LAA				
A	14	8	Nulliparous	35–51 weeks	Survival rate	24 months
B	12	14	Nulliparous	31–51 weeks	Survival rate	24 months
C	9	13	Nulliparous	31–51 weeks	Survival rate	24 months
D	8	9	Biparous	30–50 weeks	Organ weight	12 months
E	9	9	Primiparous	28–50 weeks	Survival rate	24 months
F	11	11	Biparous	28–50 weeks	Survival rate	24 months
G	11	12	Biparous	34–50 weeks	Survival rate	24 months
H	12	12	Nulliparous	29–51 weeks	Organ weight	12 months

2.3. Estrous cycles after lactation

To monitor estrous cycles after lactation, vaginal smears were also collected from rats in Cohorts D, E, F, and G from postpartum day 14. On postpartum day 22, all pups were removed from the dam. Vaginal smears were collected every day until 6 to 7 weeks after weaning. Estrous cycles were categorized every 2-week observation period as a 4-day cycle, mixed 4- and 5-day cycle, 5-day cycle, or abnormal cycle, which included long cycles and persistent estrus.

2.4. Estrous cycles after pseudopregnancy

To monitor estrous cycles after pseudopregnancy, vaginal smears were collected from extra nulliparous rats in each line after mating with vasectomized male rats. Vaginal smears were collected until 8 weeks after pseudopregnancy. The estrous cycles were categorized every 2-week observation period as above.

2.5. Statistical analysis

To compare the differences between nulliparous and parous rats in each line, the survival curves and estrous cycling trends were evaluated by Kaplan-Meier analysis with log rank test. The estrous cycling types and necropsy findings were analyzed by Fisher's exact test. The organ weights were analyzed by Student's *t*-test. A significant level of $p < 0.05$ was used for statistical analyses.

3. Results

3.1. Effects of pregnancy experience on ovarian senescence

The percentages of females with normal estrous cycles and types of estrous cycles for HAA and LAA lines are shown in Figs. 1 and 2, respectively. In the HAA line, the percentage of females with normal cycles and types of estrous cycles did not differ between the nulliparous and parous rats at each observation period. In the LAA line, abnormal cycles occurred later in parous rats than in nulliparous rats. In particular, the onset of persistent estrus and constant diestrus occurred later in parous rats. In LAA parous rats, the percentage of females with normal cycles decreased sharply in Cohort E from 32 to 34 weeks of age. It may be that onset of reproductive senescence occurred earlier in primiparous rats than biparous rats.

3.2. Effects of pregnancy experience on survival rate

Survival curves for the HAA and LAA lines are shown in Fig. 3. In the HAA line, the survival rate at 24 months of age was higher in parous (52%) than in nulliparous (40%) rats, and the median survival of parous rats (729 days and over) was longer than that of nulliparous rats (673 days). There was, however, no significant difference between parous and nulliparous rats ($p = 0.287$, Kaplan-Meier log rank analysis). In the LAA line, the survival rate at 24 months of age was similar between parous (50%) and nulliparous (54%) rats ($p = 0.935$, Kaplan-Meier log rank analysis).

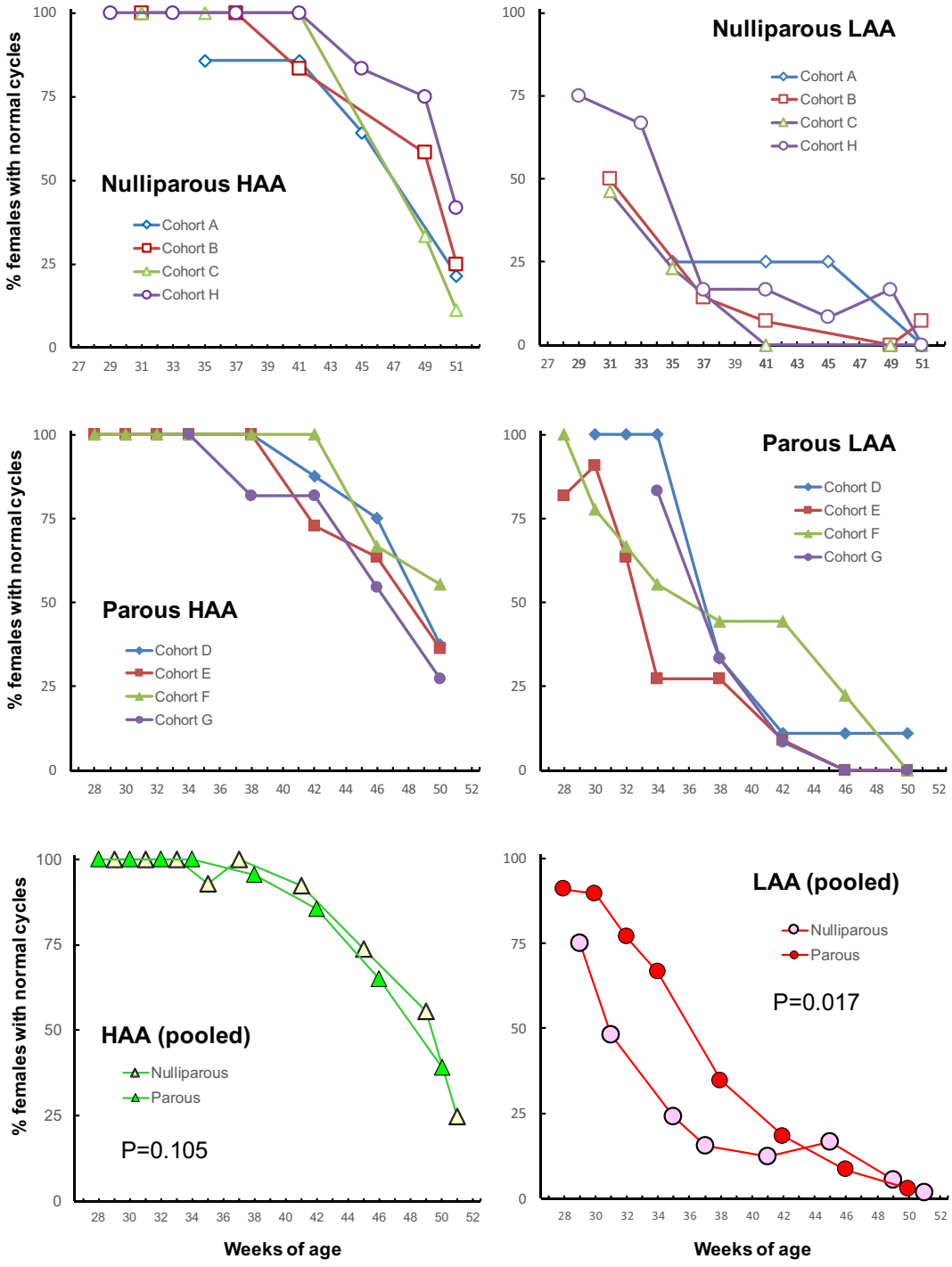

Fig. 1. Effects of pregnancy experience on the percentage of females with normal estrous cycles in the HAA and LAA lines. Upper graphs indicate individual data for nulliparous rats (Cohorts A, B, C and H) in the HAA and LAA lines. Middle graphs indicate individual data for parous rats (Cohorts D, E, F, and G) in the HAA and LAA lines. Lower graphs indicate pooled data for nulliparous and parous rats in each line. *P* values indicate differences between nulliparous and parous rats in each line by Kaplan-Meier log rank test.

3.3. Effects of pregnancy experience on tumor development

The macroscopic necropsy findings in the HAA and LAA lines are shown in Table 2. In the HAA line, a pituitary tumor mass was found in 28 of the 35 nulliparous rats (80.0%) and in 27 of the 31 parous rats (87.1%). In the LAA line, the frequency of a mammary tumor mass was markedly lower in parous rats (18.8%) than in nulliparous rats (71.4%). A decreased frequency of a mammary tumor mass in parous rats was also observed in the HAA line. Constipation with megacolon was frequently observed in parous rats (40.6%) in the LAA line.

3.4. Effects of pregnancy experience on organ weights at 52 weeks of age

Organ weights measured at 52 weeks of age are shown in Fig. 4. The pituitary was significantly heavier in parous rats than in nulliparous rats in both the HAA and LAA lines. The weight of the adrenal glands was significantly lighter in parous rats than in nulliparous rats but only in the LAA line. In the LAA line, the weight of the ovaries in parous rats

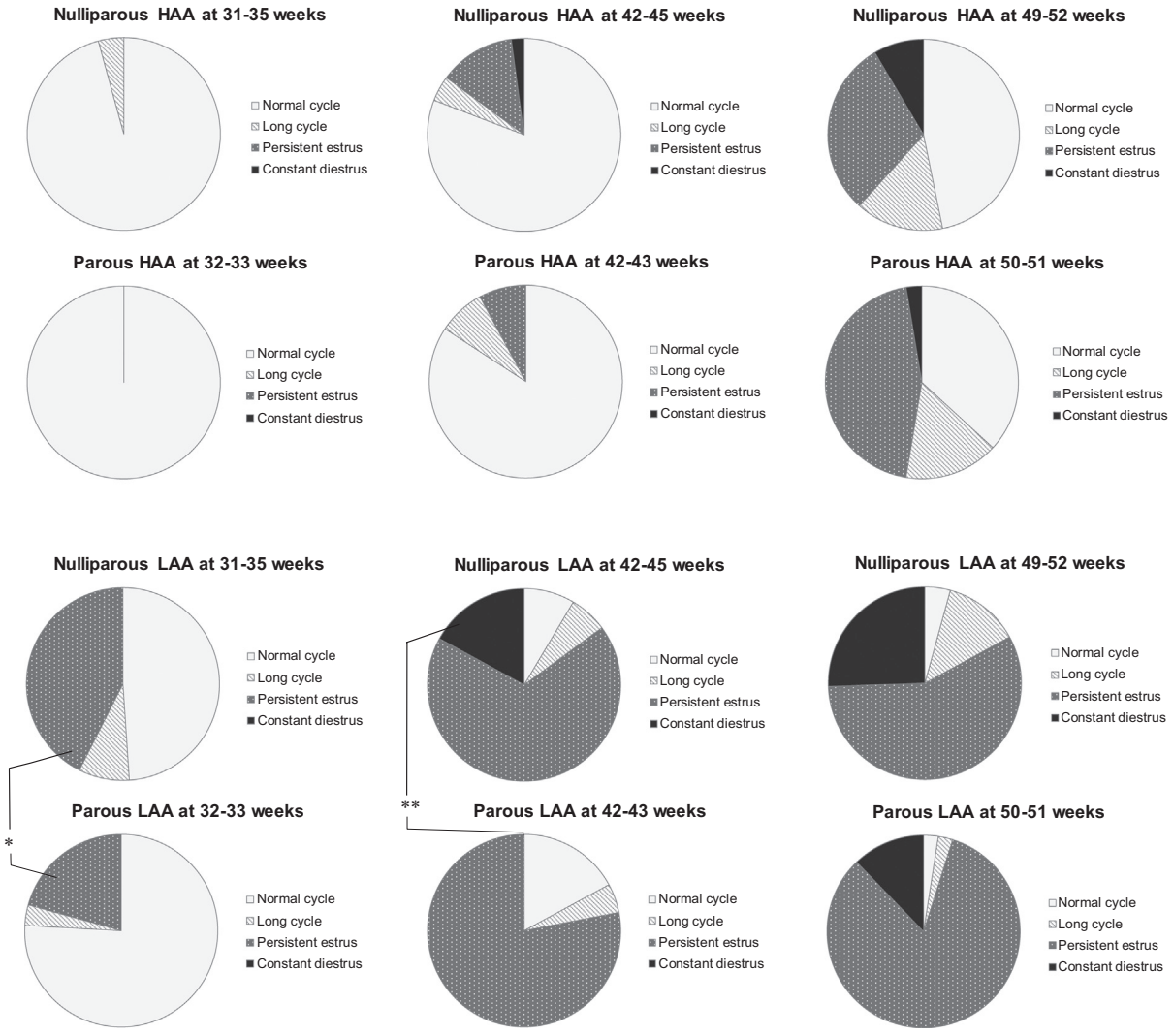

Fig. 2. Effects of pregnancy experience on the types of estrous cycles in the HAA and LAA lines. Upper graphs indicate pooled data in the HAA line for nulliparous (Cohorts A, B, C and H) and parous (Cohorts D, E, F, and G) rats at each age. Lower graphs indicate pooled data in the LAA line for nulliparous (Cohorts A, B, C, and H) and parous (Cohorts D, E, F, and G) rats at each age. Asterisks indicate significant differences based on a Fisher's exact test (*$p < 0.05$, **$p < 0.01$).

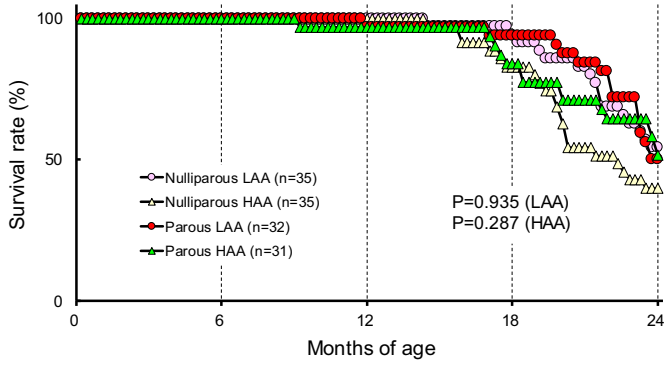

Fig. 3. Effects of pregnancy experience on survival curves in the HAA and LAA lines. Survival curves indicate pooled data for nulliparous (Cohorts A, B, C, and H) and parous (Cohorts D, E, F, and G) rats in each line. *P* values indicate differences between nulliparous and parous rats in each line by Kaplan-Meier log rank test.

was lighter than in nulliparous rats, but the difference was not significant. There were no significant differences in the terminal body weight between parous and nulliparous rats in either line.

3.5. Estrous cycles after lactation and pseudopregnancy

Estrous cycles after lactation in the HAA and LAA lines are shown in Fig. 5. In the LAA line, the percentage of females with 4-day cycles was 100% at 1–2 weeks, 67% at 3–4 weeks, 33% at 5–6 weeks, and 0% at 7–8 weeks after lactation. In the HAA line, all females had regular 4-day cycles from 1–2 weeks to 7–8 weeks after lactation.

Estrous cycles after pseudopregnancy in the LAA line are shown in Fig. 6. In the LAA line, the percentage of females with 4-day cycles was 100% at 2–3 weeks, 60% at 4–5 weeks, and 40% at 6–7 weeks of pseudopregnancy. In the HAA line, all females had regular 4-day cycles from 2–3 weeks to 6–7 weeks of pseudopregnancy (data not shown).

4. Discussion

We investigated the effects of pregnancy experience on ovarian senescence and longevity using two inbred strains of rats, which have differences in ovarian aging and lifespan. In the HAA line with a shorter lifespan, parous rats had similar ovarian senescence but increased longevity compared with nulliparous rats. In the LAA line with a longer lifespan, parous rats had a delayed onset of ovarian senescence but no gain in longevity compared with nulliparous rats.

The shortened lifespan in female HAA rats is caused by growth of a

Table 2
Summary of the macroscopic findings in the HAA and LAA lines.

	HAA				LAA			
	Nulliparous (n = 35)		Parous (n = 31)		Nulliparous (n = 35)		Parous (n = 32)	
	Number	%	Number	%	Number	%	Number	%
Eyeball								
Cataract	0	(0.0)	0	(0.0)	2	(5.7)	2	(6.3)
Lung								
Dark reddish	7	(20.0)	5	(16.1)	9	(25.7)	3	(9.4)
Atelectasis	0	(0.0)	2	(6.5)	0	(0.0)	0	(0.0)
Pituitary								
Tumor mass	28	(80.0)	27	(87.1)	17	(48.6)	15	(46.9)
Esophagus								
Narrowing	0	(0.0)	1	(3.2)	0	(0.0)	0	(0.0)
Kidney								
Dilatation pelvis	33	(94.3)	28	(90.3)	0	(0.0)	0	(0.0)
Rough surface/pale/yellowish	0	(0.0)	1	(3.2)	19	(54.3)	18	(56.3)
Cyst	0	(0.0)	1	(3.2)	4	(11.4)	0	(0.0)
Heart								
Whitish area	2	(5.7)	4	(12.9)	3	(8.6)	1	(3.1)
Enlargement	1	(2.9)	3	(9.7)	0	(0.0)	0	(0.0)
Liver								
Enlargement	0	(0.0)	3	(9.7)	4	(11.4)	0	(0.0)
Recessed area	0	(0.0)	0	(0.0)	2	(5.7)	1	(3.1)
Pale colored	2	(5.7)	0	(0.0)	2	(5.7)	2	(6.3)
Small	0	(0.0)	0	(0.0)	1	(2.9)	1	(3.1)
Dark colored area	3	(8.6)	1	(3.2)	3	(8.6)	1	(3.1)
Spleen								
Enlargement	3	(8.6)	1	(3.2)	3	(8.6)	3	(9.4)
Small	1	(2.9)	0	(0.0)	1	(2.9)	4	(12.5)
Stomach								
Tumor mass	0	(0.0)	1	(3.2)	0	(0.0)	0	(0.0)
Thickening mucosa	2	(5.7)	0	(0.0)	2	(5.7)	1	(3.1)
Recessed area	3	(8.6)	1	(3.2)	0	(0.0)	0	(0.0)
Lymph node, mesenteric								
Enlargement	1	(2.9)	1	(3.2)	1	(2.9)	0	(0.0)
Mesenteric artery								
Bead-like nodules	0	(0.0)	0	(0.0)	4	(11.4)	5	(15.6)
Abdominal cavity								
Ascites	2	(5.7)	1	(3.2)	2	(5.7)	0	(0.0)
Adrenal gland								
Enlargement	7	(20.0)	7	(22.6)	13	(37.1)	13	(40.6)
Thyroid grand								
Enlargement	2	(5.7)	2	(6.5)	0	(0.0)	1	(3.1)
Parathyroid gland								
Enlargement	1	(2.9)	0	(0.0)	6	(17.1)	3	(9.4)
Uterus								
Tumor mass	1	(2.9)	1	(3.2)	1	(2.9)	0	(0.0)
Polyp	0	(0.0)	3	(9.7)	8	(22.9)	1	(3.1) *
Mammary gland								
Tumor mass	14	(40.0)	6	(19.4)	25	(71.4)	6	(18.8) **
Galactocele	1	(2.9)	1	(3.2)	1	(2.9)	0	(0.0)
Ovary								
Cyst	2	(5.7)	4	(12.9)	1	(2.9)	0	(0.0)
Tail								
Tumor mass	0	(0.0)	1	(3.2)	0	(0.0)	0	(0.0)
Intestine								
Constipation/megacolon	0	(0.0)	1	(3.2)	2	(5.7)	13	(40.6) **

Asterisks indicate significant differences from the incidences of nulliparous rats in each line (*$p < 0.05$, **$p < 0.01$ by Fisher's exact test).

pituitary tumor, which compresses the cerebral base (Ohta et al., 2016). In the HAA line, lifespan lengthened in parous rats compared with nulliparous rats, but there was no difference in the frequency of pituitary tumors. These results suggest that pituitary tumors in the HAA line may develop slower in parous rats compared with nulliparous rats, and contrasts with a recent study showing that pregnancy may promote pituitary tumor growth in mice (Yin and Qi, 2017).

In the LAA line, the onset of ovarian senescence was delayed in parous rats compared with nulliparous rats. Furthermore, estrous cycles after lactation in the LAA line changed from 5-day to 4-day cycles, which was also observed in LAA pseudopregnant rats. Females in the HAA line have a regular 4-day estrous cycle, but most females in the LAA line have a regular 5-day estrous cycle (Asai et al., 2002). A prolonged elevation in plasma progesterone and a higher elevation in plasma prolactin surge are characteristics of the LAA line with 5-day estrous cycles (Asai et al., 2002). In lactating rats, ovarian function is inhibited by suckling from offspring, and follicular development in the ovary is suppressed (Taya and Greenwald, 1982). Female rats resume estrous cycling 2–5 days after their pups have been weaned, and prolactin surges decrease in parous rats compared with nulliparous rats (Bridges et al., 1993). Therefore, decreased prolactin surges may be caused by pregnancy experience, which delays the onset of ovarian senescence in the LAA line.

Although the frequency of mammary tumors in the LAA line was

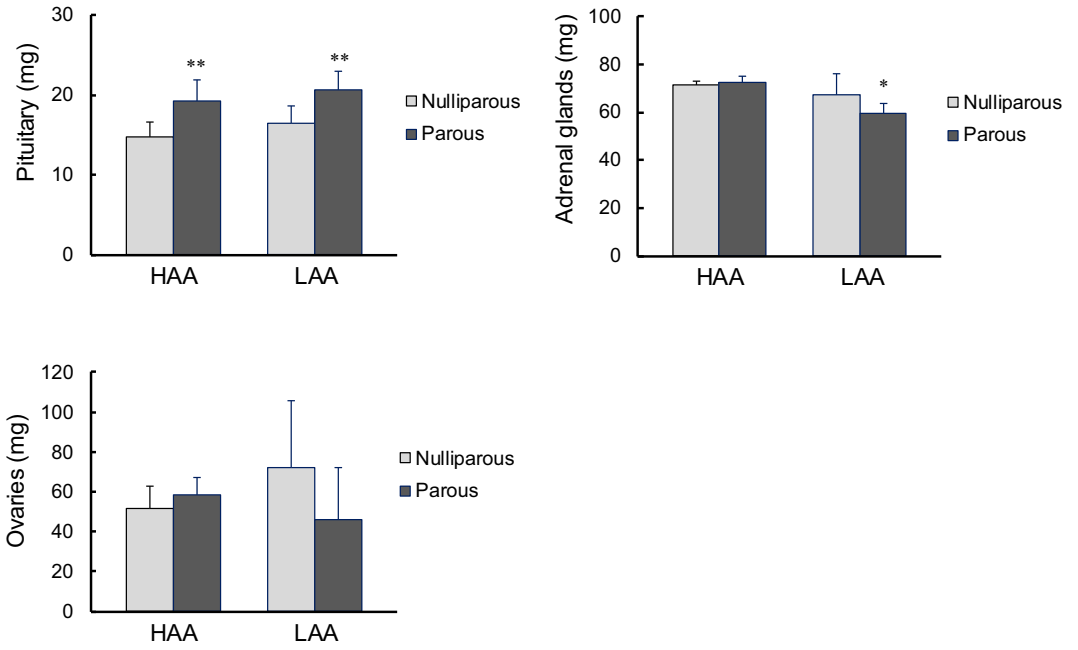

Fig. 4. Effects of pregnancy experience on organ weights in the HAA and LAA lines at 52 weeks of age. Values are expressed as means + S.D. of nulliparous (Cohort H) and parous (Cohort D) rats in each line. Asterisks indicate significant differences based on a Student's *t*-test when compared with nulliparous rats (*$p < 0.05$, **$p < 0.01$).

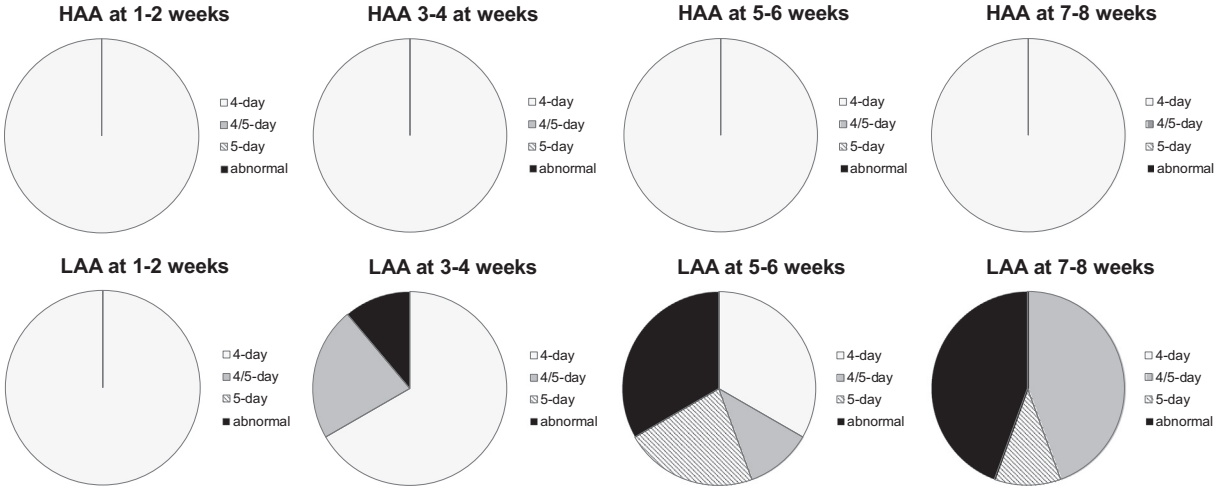

Fig. 5. Estrous cycles after lactation in the HAA and LAA lines. Upper and lower graphs indicate changes of estrous cycles after the second lactation in the HAA and LAA lines (both in Cohort D), respectively.

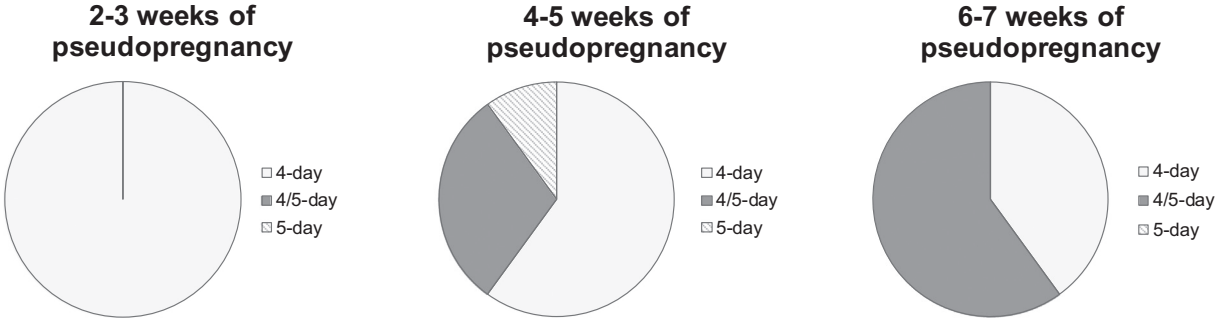

Fig. 6. Estrous cycles after pseudopregnancy in the LAA line. Graphs indicate changes of estrous cycles after pseudopregnancy in the LAA line.

markedly decreased in parous rats compared with nulliparous rats, there was no difference in longevity. Mammary tumors are quite common in the LAA line, which may be caused by high levels of plasma prolactin (Ohta et al., 2016). Parous rats have a lower incidence of mammary tumors induced by chemical carcinogens compared with nulliparous rats (Thordarson et al., 1995). A decreased frequency of mammary tumors in parous rats was also observed in the HAA line. These results suggested that both chemically induced and spontaneous tumor development in mammary glands are mitigated by pregnancy experience. However, the lifespan of parous rats did not increase despite a large decline in mammary tumors because of an increased frequency of constipation with megacolon in the LAA line. The origin of constipation in LAA parous rats is unknown, but may be caused by reduced intestinal motility during aging related to characteristics of the LAA line such as low locomotor activity (Ohta et al., 1995). These results suggest that hormonal changes related to pregnancy experience resulted in the development of other diseases instead of endocrine tumors.

At 52 weeks of age, the pituitary weight of parous rats was heavier than that of nulliparous rats in both the HAA and LAA lines, which suggests that hyperplasia of lactotrophs in response to high plasma estrogen during pregnancy remained in both lines after lactation. The adrenal weight of parous rats was lighter than that of nulliparous rats only in the LAA line, which had ovarian senescence. In humans, estrogen production is replaced by adrenal androgens, such as dehydroepiandrosterone (DHEA), during menopause transition (Lasley et al., 2013). Although plasma levels of DHEA are low in rats (van Weerden et al., 1992), the LAA line may still be useful for analyzing ovarian adrenal interactions during menopause. In the LAA line, the ovarian weight of parous rats was lighter than that of nulliparous rats. Ovaries are heavier in the LAA than in the HAA line because of an increased number of corpora lutea (Asai et al., 2002). Therefore, a decrease in corpora lutea in LAA parous rats may explain the delayed onset of ovarian senescence.

In cohort studies, the relationship between reproductive factors and longevity is confounded by non-reproductive factors such as smoking habits, obesity, education levels, and nutrition status (Merritt et al., 2015). Therefore, it is important to develop animal models to analyze the relationship between reproductive factors and longevity. There are individual differences in female reproductive factors, such as puberty, menstrual cycle, and menopause onset, in humans and experimental animals. Furthermore, individual differences are also observed in longevity. The HAA and LAA lines have clearly different baselines for reproductive factors, and there is little individual variation within lines. Compared to females in the LAA line, females in the HAA line show early puberty (Shirota et al., 2004), regular 4-day estrous cycles (Asai et al., 2002), and later senescence (Ohta et al., 2016). These data are within the normal range of variation for Sprague-Dawley rats from which the two lines originate. However, degree of earlier reproductive senescence in the LAA line may correspond to premature ovarian failure (POF) in women. Although several genes are reported as having significance in POF (Dixit et al., 2010), their role in ovarian physiology is not known. A premutation in the fragile-X mental retardation (FMR1) gene is the most commonly known congenital cause of POF (Goswami and Conway, 2007), and the FMR1 knockout mice show poor learning in passive avoidance task (Ding et al., 2014). Therefore, the LAA line may be useful as a POF animal model to understand genetic basis and its impact on ovarian physiology.

In conclusion, delayed onset of reproductive senescence induced by pregnancy experience was observed only in the LAA line where estrous cycles after lactation changed from 5-day to 4-day cycles. On the other hand, increased longevity induced by pregnancy experience was observed only in the HAA line where the development of the pituitary tumor was delayed. Thus, inbred strains, such as HAA and LAA lines, are a useful tool to analyze the relationship between reproductive factors and longevity.

Conflict of interest

The authors declare that there is no conflict of interest.

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References

Akieda-Asai, S., Ohta, R., Shirota, M., Jaroenporn, S., Watanabe, G., Taya, K., 2011. Endocrinological differences between Hatano high- and low-avoidance rats during early two-way avoidance acquisition. Exp. Anim. 60, 509–516.
Asai, S., Ohta, R., Shirota, M., Sato, M., Watanabe, G., Taya, K., 2002. Reproductive endocrinology in Hatano high- and low-avoidance rats during the estrous cycle. Endocrine 18, 161–166.
Asai, S., Ohta, R., Shirota, M., Watanabe, G., Taya, K., 2004. Differential responses of the hypothalamo-pituitary-adrenocortical axis to acute restraint stress in Hatano high- and low-avoidance rats. J. Endocrinol. 81, 515–520.
Asai, S., Ohta, R., Fujikawa, T., Sakai, R.R., Shirota, M., Ogata, M., Watanabe, G., Taya, K., 2006. Gastric ulceration and expression of prolactin receptor in the brain in Hatano high- and low-avoidance rats. Endocrine 30, 161–166.
Barha, C.K., Hanna, C.W., Salvante, K.G., Wilson, S.L., Robinson, W.P., Altman, R.M., Nepomnaschy, P.A., 2016. Number of children and telomere length in women: a prospective, longitudinal evaluation. PLoS One 11, e0146424.
Barrett, E.L., Richardson, D.S., 2011. Sex differences in telomeres and lifespan. Aging Cell 10, 913–921.
Behl, C., Widmann, M., Trapp, T., Holsboer, F., 1995. 17-beta estradiol protects neurons from oxidative stress-induced cell death in vitro. Biochem. Biophys. Res. Commun. 216, 473–482.
Bridges, R.S., Felicio, L.F., Pellerin, L.J., Stuer, A.M., Mann, P.E., 1993. Prior parity reduces post-coital diurnal and nocturnal prolactin surges in rats. Life Sci. 53, 439–445.
Ding, Q., Sethna, F., Wang, H., 2014. Behavioral analysis of male and female Fmr1 knockout mice on C57BL/6 background. Behav. Brain Res. 271, 72–78.
Dixit, H., Rao, L., Padmalatha, V., Raseswari, T., Kapu, A.K., Panda, B., Murthy, K., Tosh, D., Nallari, P., Deenadayal, M., Gupta, N., Chakrabarthy, B., Singh, L., 2010. Genes governing premature ovarian failure. Reprod. BioMed. Online 20, 724–740.
Finch, C.E., 2014. The menopause and aging, a comparative perspective. J. Steroid Biochem. Mol. Biol. 142, 132–141.
Finch, C.E., Felicio, L.S., Mobbs, C.V., Nelson, J.F., 1984. Ovarian and steroidal influences on neuroendocrine aging processes in female rodents. Endocr. Rev. 5, 467–497.
Goswami, D., Conway, G.S., 2007. Premature ovarian failure. Horm. Res. 68, 196–202.
Guzman, R.C., Yang, J., Rajkumar, L., Thordarson, G., Chen, X., Nandi, S., 1999. Hormonal prevention of breast cancer: mimicking the protective effect of pregnancy. Proc. Natl. Acad. Sci. U. S. A. 96, 2520–2525.
Ilango, A., Shumake, J., Wetzel, W., Scheich, H., Ohl, F.W., 2012. The role of dopamine in the context of aversive stimuli with particular reference to acoustically signaled avoidance learning. Front. Neurosci. 6, 132.
Jaroenporn, S., Horii, Y., Akieda-Asai, S., Wang, K., Nagaoka, K., Ohta, R., Shirota, M., Watanabe, G., Taya, K., 2011. Endocrine mechanisms responsible for different follicular development during the estrous cycle in Hatano high- and low-avoidance rats. J. Reprod. Dev. 57, 690–699.
Kelsey, J.L., 1993. Breast cancer epidemiology: summary and future directions. Epidemiol. Rev. 15, 256–263.
Lasley, B.L., Crawford, S.L., McConnell, D.S., 2013. Ovarian adrenal interactions during the menopausal transition. Minerva Ginecol. 65, 641–651.
Levine, M.E., Lu, A.T., Chen, B.H., Hernandez, D.G., et al., 2016. Menopause accelerates biological aging. Proc. Natl. Acad. Sci. U. S. A. 113, 9327–9332.
MacMahon, B., Cole, P., Lin, T.M., Lowe, C.R., Mirra, A.P., Ravnihar, B., Salber, E.J., Valaoras, V.G., Yuasa, S., 1970. Age at first birth and breast cancer risk. Bull. World Health Organ. 43, 209–221.
Merritt, M.A., Riboli, E., Murphy, N., Kadi, M., et al., 2015. Reproductive factors and risk of mortality in the European prospective investigation into cancer and nutrition; a cohort study. BMC Med. 13, 252.
Musey, V.C., Collins, D.C., Musey, P.I., Martino-Saltzman, D., Preedy, J.R., 1987. Long-term effect of a first pregnancy on the secretion of prolactin. N. Engl. J. Med. 316, 229–234.
Ohta, R., Matsumoto, A., Hashimoto, Y., Nagao, T., Mizutani, M., 1995. Behavioral characteristics of rats selectively bred for high and low avoidance shuttlebox response. Congenit. Anom. 35, 223–229.
Ohta, R., Shirota, M., Adachi, T., Tohei, A., Taya, K., 1999. Plasma ACTH levels during early, two-way avoidance acquisition in high- and low-avoidance rats (Hatano strains). Behav. Genet. 29, 137–144.
Ohta, R., Kumagai, F., Marumo, H., Usumi, K., Saito, Y., Kuwagata, M., 2016. Stress-reactive rats (high-avoidance female rats) have a shorter lifespan than stress-non-reactive rats (low-avoidance female rats). J. Toxicol. Pathol. 29, 77–84.
Rajkumar, L., Guzman, R.C., Yang, J., Thordarson, G., Talamantes, F., Nandi, S., 2001. Short-term exposure to pregnancy levels of estrogen prevents mammary carcinogenesis. Proc. Natl. Acad. Sci. U. S. A. 98, 11755–11759.
Shirota, M., Sato, M., Kojima, K., Ohta, R., 2004. Minor involvement of somatic growth in the onset of puberty of Hatano high- and low-avoidance rats. Reproduction 127,

389–395.
Sun, F., Sebastiani, P., Schupf, N., Bae, H., Andersen, S.L., McIntosh, A., Abel, H., Elo, I.T., Perls, T.T., 2015. Extended maternal age at birth of last child and women's longevity in the long life family study. Menopause 22, 26–31.
Taya, K., Greenwald, G.S., 1982. Mechanisms of suppression of ovarian follicular development during lactation in the rat. Biol. Reprod. 27, 1090–1101.
Thordarson, G., Jin, E., Guzman, R.C., Swanson, S.M., Nandi, S., Talamantes, F., 1995. Refractoriness to mammary tumorigenesis in parous rats: is it caused by persistent changes in the hormonal environment or permanent biochemical alterations in the mammary epithelia? Carcinogenesis 16, 2847–2853.
van Weerden, W.M., Bierings, H.G., van Steenbrugge, G.J., de Jong, F.H., Schröder, F.H., 1992. Adrenal glands of mouse and rat do not synthesize androgens. Life Sci. 50, 857–861.
Wu, X., Cai, H., Kallianpur, A., Gao, Y.T., Yang, G., Chow, W.H., Li, H.L., Zheng, W., Shu, X.O., 2014. Age at menarche and natural menopause and number of reproductive years in association with mortality: results from a median follow-up of 11.2 years among 31,955 naturally menopausal Chinese women. PLoS One 9, e103673.
Yin, C., Qi, X., 2017. Pregnancy promotes pituitary tumors by increasing the rate of the cell cycle. Oncol. Lett. 14, 4873–4877.