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Life Spans in Mice From Strains Selected for High or Low Aggression

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The present study assessed the life spans in two lines of mice selectively bred for high (Turku Aggressive, TA) and low (Turku Nonaggressive, TNA) levels of aggression. The maintained parental Swiss albino strain (N), normally distributed with regard to aggression, served as a control line. It was found that the TNA males had a significantly shorter life span than the other lines of mice of both sexes. The relative early death of the TNA males was discussed in terms of male age-related decline of inherited low levels of catecholamine and androgenous hormone concentrations.

Key words: aggression, life span, mice, selective breeding

INTRODUCTION

Lagerspetz [1961] originated a mouse selection experiment in 1959 from an outbred Swiss albino stock relatively normally distributed for aggressiveness. The experiment resulted in two lines of mice carefully chosen for high (Turku Aggressive [TA]) and low (Turku Nonaggressive [TNA]) levels of aggressiveness [Lagerspetz, 1964]. The TA and TNA mice have been investigated from many conceivable angles for more than 60 generations, but their mean life spans are now for the first time assessed. Neurochemical and endocrinological characteristics of TA and TNA males belonging to the 13th and 14th generations of the selection were examined by Lagerspetz et al. [1968] who indicated interstrain differences in catecholamines and indolamine. TA mice had 11% more noradrenaline in the brain stems than TNA mice. The importance of noradrenaline for the effector manifestation of aggressive behavior has been stressed by Allikmets [1974]. In contrast, nonaggressivity is associated with enhanced levels of indolamine and Lagerspetz et al. [1968] found 19% more 5-hydroxytryptamine content in the forebrain of the TNA animals. Also, the adrenaline contents of the adrenal glands of the strains were examined and found to be higher ($P < .05$) in TA males. These

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findings imply strain differences in the character in the sympathetic branch of the autonomic nervous system and hint at distinct central arousal states in animals varying in levels of aggression. Noradrenergic activation bears effects on many parameters, e.g., longevity [Kvist, 1985, 1989; Slater et al., 1977; Stavnes, 1975]. However, noradrenaline concentrations in male rodents are found to decrease with increasing age. In contrast, females do not exhibit an age-related decline in noradrenaline content [Martinez et al., 1981].

Archer [1991] causally linked levels of aggression and concentrations of testosterone in male rodents. Further, a link between male testosterone concentration, survival, and longevity has been established by several researchers [e.g., Dessi-Fulgehri et al., 1976; Elias and Elias, 1977; Zielinski and Vandenbergh, 1993]. Concentration of rodent male testosterone is found to be age related; it declines with increasing age [Chambers et al., 1991; Bethea and Walker, 1979; Elias and Elias, 1975; Miller and Riegle, 1982; Perheentupa, 1994]. Lagerspetz et al. [1968] indicated that the testes of the TA males were heavier (26–32%) than those of the TNA males ($P < .001$). No interstrain difference was found between the mean weights of the seminal vesicles and the number or size of the interstitial cells. The larger amount of tubular material in the testes of the TA males was thought to be a function of strain differences in the production of the follicle-stimulating hormone (FSH) [Lagerspetz et al., 1968]. FSH dissimilarities are reflected in TA females as a shorter estrous cycle compared to that of TNA females ($P < .05$) [Kvist, 1992]. Even in female rodents with a normal distribution of aggressive responses, testosterone treatment was found to be more effective than estradiol in enhancing competitive agonistic behavior. Female plasma levels of testosterone comprise, though, only a fraction of those normally found in males [Haug et al., 1992; Sandnabba et al., 1994; Zielinski and Vandenbergh, 1991]. Since physiological and behavioral, both interstrain, as well as sex dissimilarities are evident in the TA and TNA mice [Lagerspetz and Lagerspetz, 1971, 1974, 1975; Lagerspetz et al., 1968], it is reasonable to suggest that there are both interstrain and sex differences with regard to their life spans.

GENERAL METHODS

Subjects

One hundred thirty-nine mice (70 females and 69 males) were used in the present study. The mice belonged to the 52nd and 57th generations (S_{52} and S_{57}) of two selectively bred lines of high (TA) and low (TNA) levels of aggressiveness [Lagerspetz, 1964]. The unselected normal (N) strain always served as a control for the selected lines. All mice were bred, reared, and mated once in the laboratory at Åbo Akademi University. The animals were tested for aggressiveness according to the method used by Lagerspetz [1964]. She applied a 7-min seven-point rating scale with a reliability coefficient of .87 for measuring male aggressiveness by means of standard dyadic tests when the mice were approximately 3 months of age.

Housing

The mice were weaned at 4 weeks of age and then individually housed in wire-topped laboratory polycarbonate cages measuring 13.5 × 23.5 × 13.0 cm. The mice were bred in a noiseless room on a 12 hr light/12 hr dark cycle with a room temperature of approximately 22°C and with 45% humidity. The animals were fed standard laboratory

pellets R3 from Lactamin, Stockholm, Sweden (1,260 kj/100 g: 5% animal fat, 21% protein) as well as tap water ad libitum. At the age of 1½ years, the mice participating in Experiment I retired to a separate room with identical housing conditions in order to minimize the risk of any harmful contagion interfering with their natural death.

Procedure

In Experiment I, the animals were inspected about three times a week during their entire life span. In Experiment II, at the age of 1 year, the animals were transferred to an adjacent experimental room when their metabolism was recorded. The metabolism was studied as follows: The cages were cleaned and the sawdust renewed and weighed. The animals were deprived of pellets for 12 hr but water was available ad libitum. The mice were then given access to preweighed food for a period of 72 hr after which time the remaining food was reweighed. By comparing the weight of the sawdust in the cages before and after the test period, a measure of excretion (i.e., defecation and urination) was established [Hansen and Ferreira, 1986].

EXPERIMENT I: THE LIFE SPANS OF TA, TNA, AND N MICE

The life span in days was determined for mice of the 52nd generation of the two selectively bred strains. Ten TA and 10 TNA females and 12 TA and 12 TNA males participated in Experiment I. Nine N females and 10 N males served as controls.

Results

Figure 1 shows the mean life span in days of the TNA, N, and TA females. The 50% surviving point is about 700 days for the N females but about 900 days for TNA and TA females. Figure 2 shows that the 50% surviving point for the TNA males is close to 500 days as opposed to that of the TA and N males, which is more than 800 days.

Significant life span differences between strains and sexes are indicated in Table I. The TNA males are the least fit for survival as opposed to the TNA females which

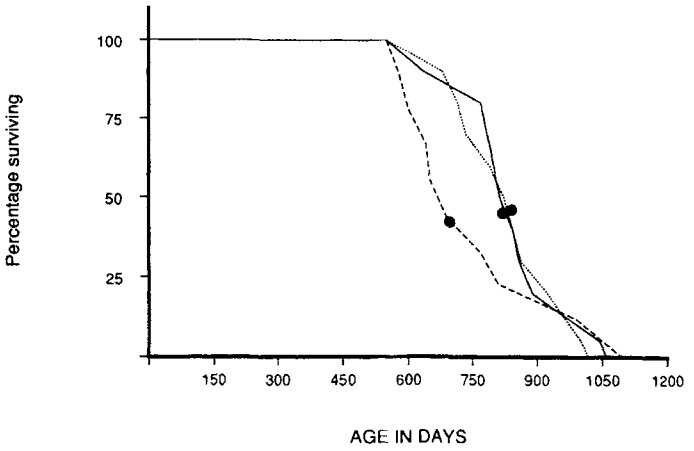

Fig. 1. Survival curves for female mice of TNA, N, and TA strains. Filled circles indicate 50% surviving. Unbroken line, TNA females; dashed line, N females; dotted line, TA females.

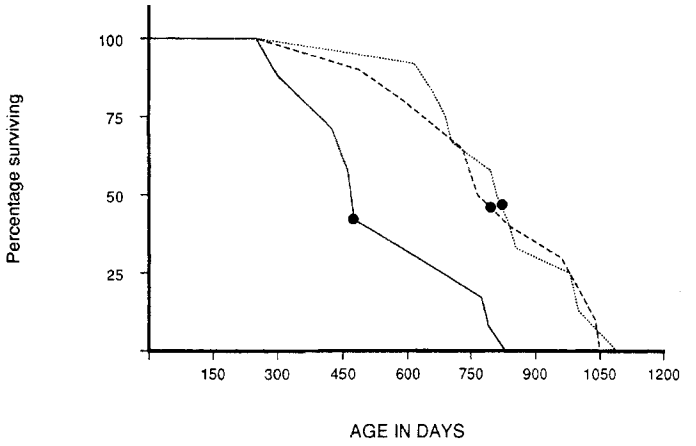

Fig. 2. Survival curves for male mice of TNA, N, and TA strains. Filled circles indicate 50% surviving. Unbroken line, TNA males; dashed line, N males; dotted line, TA males.

exhibit the longest life spans. However, females do not differ significantly from each other in this respect. The life spans of the TA and N females do not differ from those of their male counterparts either.

EXPERIMENT II: THE METABOLISM OF THE TA, TNA, AND N MICE

Mice from the 57th generation of the two selectively bred strains as well as animals from the N strain were tested with regard to their metabolism at the age of 12 months. Thirteen TA and 13 TNA females, 15 TA (aggressiveness scores 6.4, SD 0.6) and 15 TNA males (aggressiveness scores 1.2, SD 0.5) as well as 10 N females and 10 N males participated in Experiment II.

Results

The results of Experiment II are indicated in Figure 3. The TNA females had a greater food intake and excreted more than the other groups of females. Of the male groups compared to each other, TA and TNA mice had an equal and a greater food intake compared to that of the N male group. The latter group also excreted less than the two former groups.

TABLE I. Life Span Differences Between Males and Females of the TNA, N, and TA Strains†

			Age (days)			ANOVA	TNA ♂ <	
Strain	Sex	n	M	(SE)	Range	[df1,df2]	F	t
TNA	Male	12	534.2	(53.2)	300-830			
N	Male	10	821.0	(61.5)	485-1040	[2, 31]	10.61***	3.51**
TA	Male	12	836.3	(44.4)	615-1090			433****
TNA	Female	10	849.0	(38.7)	635-1045			4.56****
N	Female	9	758.3	(59.8)	580-1095	[2, 26]	1.17	2.77*
TA	Female	10	838.5	(35.9)	680-1005			4.51****

†$P < .01$, **$P < .005$, ***$P < .001$, ****$P < .0005$.

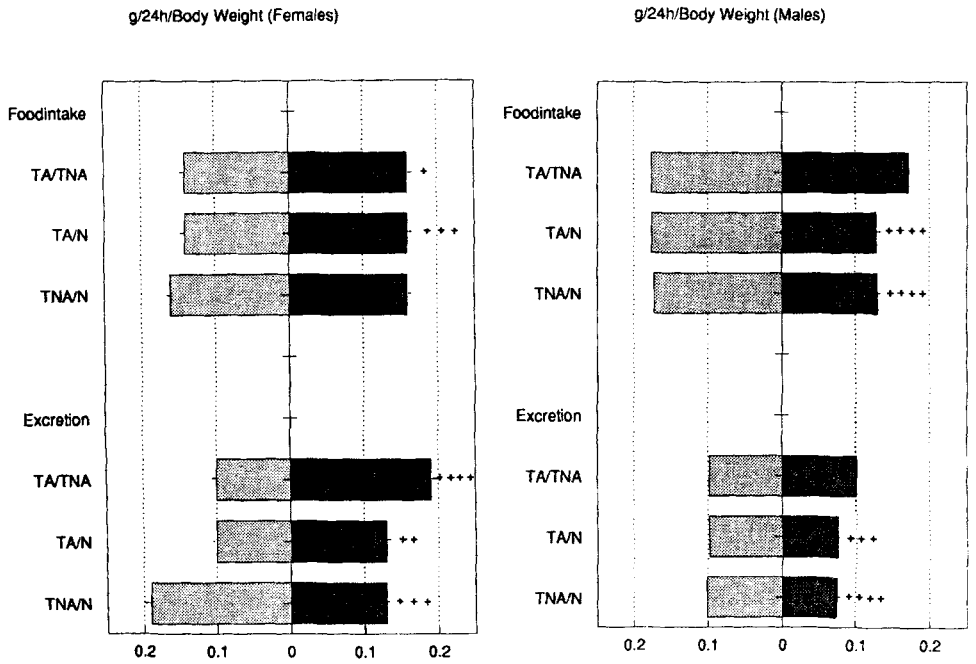

Fig. 3. *Food intake and excretion (g/24h/body weight) in females and males of the* TNA, N, *and* TA strains. +, $P < .025$; ++, $P < .01$; +++, $P < .005$; ++++, $P < .0005$.

DISCUSSION

Both interstrain and sex dissimilarities in longevity of TA and TNA mice were found. The typical mean longevity of a laboratory mouse ranges from 1.3 to 3 years [Russell, 1966]. Rodent longevity differs with regard to breeding history including factors such as selection for a specific trait, inbreeding, nutritional and housing conditions. The present data fell between the characteristic limits and yielded mean life spans ranging from approximately 1.5 to 2.8 years. The TNA males had the shortest lifetime, a fact that contributed to the body of the growing evidence of the lower vitality of the TNA males [Kvist, 1989; Lagerspetz, 1964; Selander and Kvist, 1991]. In contrast, no sign of depressed vitality was observed in the much-less investigated TNA females who outlived all other presently recorded groups of mice. When considering this fact, one has to bear in mind that intermale and interfemale levels of agonistic behavior are not strong correlates of each other, although common genes may be involved [Ebert, 1983]. Female nonaggressivity per se hardly enhances the fitness for survival [e.g., Brain et al., 1992], but a nonattacking behavior in combination with a capacity to control or appropriate nourishment probably constitutes a solid basis for longevity. Lagerspetz [1964] subjected TA and TNA females to a competition for common food. No significant strain difference was found, although TNA females spent more time eating, made a greater number of eating attempts, and prevented more often partners from eating. A TNA female tendency to control resources is supported by the present data, indicating a greater food intake for TNA than TA females. The finding of the longevity of the TNA females

favors our idea that nonaggressivity combined with a tendency to exhibit control may constitute a criterion for feminine fitness for survival.

Adrenergic activation is connected to aggressive behavior [Allikmets, 1974] and sympathetic excitation [Stavnes, 1975]. These factors are useful in protection against attacks and are now linked to longevity. The TNA males were initially found to be low in orthosympathetic activity and excitability due to their low noradrenergic and adrenergic contents [Lagerspetz et al., 1968]. Since TNA males are more under the influence of parasympaticus, they are, more so than TA males, prone to react with fear [Lagerspetz, 1977] and to be affected by external cues [Benus et al., 1987], conditions which enhance stress and contribute to a shorter life span [Ottenweller et al., 1988].

Researchers [Archer, 1991; Dessi-Fulgheri et al., 1976; Elias and Elias, 1975; Parmigiani et al., 1989] have established a causal link between levels of intermale aggression and testosterone concentrations. TNA males have initially lower levels of androgenous hormones than TA males [Lagerspetz and Lagerspetz, 1975]. Testosterone therapy was administered to the former to enhance their agonistic responses [Sandnabba et al., 1994]. However, TNA males did not respond with increased agonistic behavior after neonatal and adult testosterone treatment and these males (S_{27}) were therefore thought to lack genes comprising a disposition for aggressive behavior. Other researchers [Oortmessen et al., 1987] found, in genetically different wild male mice distinct in attack latency, that individual differences in this behavior were related not only to variation in baseline plasma testosterone level but also to variation in responsiveness to testosterone that was induced before puberty. The maintenance of the attack-latency level in adult mice was independent of testosterone in fast-attacking mice but not in males reluctant to attack. The latter are presently compared to the TNA male mice.

A decrease in the production of androgen is typical of aging male laboratory rodents [Chambers et al., 1991; Elias and Elias, 1975; Perheentupa, 1994]. Bethea and Walker [1979] proposed that decreased testicular function in old male rodents may not solely be the result of a decrement in Leydig cell steroid-producing capacity, but that it may occur due to Leydig cell loss in a possible interaction with age-related changes in the brain and pituitary. Also, an alteration of endocrine control of testicular function in aging rats is a result of progressively reduced LH and testosterone secretion [Miller and Riegle, 1982]. An age-related plasma testosterone level decrement or an almost complete suppression of it may occur as a result of combination of age, stress, and disease [Ottenweller et al., 1988].

In summation, when studying the longevity of aggressive, nonaggressive, and normal Swiss albino mice of both sexes, it was observed that TNA males had the shortest life span compared to the other groups of mice. This finding was thought to be due to the selection experiment producing TNA males with initially subnormal levels of catecholamines and testosterone. It seems reasonable to assume that the male age-related decline in these concentrations is responsible for the relatively early death of the TNA males.

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