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MICE LINES DIVERGENTLY SELECTED FOR BODY MASS SHOW SIGNIFICANT DIFFERENCES IN SPATIAL LEARNING

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A b s t r a c t

The present study was aimed to investigate the influence of multigenerational selection in the direction of low or high body weight on spatial learning and memory in mice. Light and heavy lines of rodents were selected from an outbred stock constructed from inbred strains; A/St, BN/a, BALB/c and C57BL/6J. Male mice selected at weaning for the low (L, n=13) or high (H, n=16) body weight for 94 generations have been evaluated for behavioral performance and cognition in the modified Morris water maze task. The unselected control line (Con, n=15) was run in parallel. Presented results lead to the conclusion that selection of mice for high and low body weight over 94 generations resulted in a significant differentiation in learning abilities. Our findings suggest improvement of learning of the hidden platform position in heavy line of mice.

LINIE MYSZY PODDANE SELEKCJI W KIERUNKU WYSOKIEJ I NISKIEJ MASY CIAŁA RÓŻNIĄ SIĘ ZNAMIENIE W UCZENIU PRZESTRZENNYM

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S ł o w a k l u c z o w e: masa ciała, zachowanie, pamięć przestrzenna, uczenie, myszy.

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Abstrakt

Celem badania jest ocena wpływu wielopokoleniowej selekcji w kierunku niskiej lub wysokiej masy ciała na procesy uczenia się i pamięci przestrzennej u myszy. Obie linie gryzoni uzyskano w wyniku wielopokoleniowej selekcji z niekrewniaczej wsobnej hodowli myszy szczepów; A/St, BN/a, BALB/c i C57BL/6J. Zachowanie i funkcje poznawcze analizowano przy pomocy labiryntu wodnego Morrisa u 13 samców z linii lekkiej (L, n = 13) i 16 samców z linii ciężkiej (H, n = 16). Równolegle prowadzono linię kontrolną, z której do badania wybrano 15 samców (Con, n = 15). Prezentowane wyniki prowadzą do wniosku, że wielopokoleniowa selekcja myszy w kierunku wysokiej i niskiej masy ciała prowadzi do istotnego zróżnicowania w zakresie zdolności uczenia się. Nasze wyniki sugerują, że myszy z linii ciężkiej znacznie szybciej uczą się pozycji podwodnej platformy w teście labiryntu wodnego.

Introduction

Quantitative traits are conditioned by genes located on the same chromosome or on the added impact on many genes. Therefore simple selections based only on the one trait may produce changes in other functions, e.g. reproductive abilities. This phenomena may be associated with the preferential use of one gene product in regulation of expression of the others (LIU et al. 1994, REID et al. 1995).

The body weight is classified as a simple measured quantitative trait associated with multigene effects. Decades ago, correlations between body weight and longevity, processes of aging or certain physiological parameters have been proven.

So far, studies have shown that there is a relationship between body mass and life expectancy and the number of reproductive functions such as: time of puberty, gonadal weight, level of ovulation, the number of embryos, the fetus and placenta weight, litter size and mortality in the prenatal period (WIRTH-DZIECIOŁOWSKA et al. 2005). Positive correlation between this quantitative trait, fat content and size of many organs also has been found (BENIVAL et al. 1992, HASTINGS and HILL 1990, HASTINGS et al. 1991). Selection on body weight may affect also some aspects of animal behavior e.g. learning, memory and visuomotor skills. Study by Padeh and Soller (1976) demonstrated positive genetic correlations between body mass, weight of both cerebellum and cerebrum and learning abilities in inbred strains of mice.

This study focuses on the behavioral and cognitive processes in mice selected up to 94 generations in two lines with low and high body mass. The aim of our experiment was to examine the correlation between body weight the chosen lines of mice and spatial learning, memory, motivation and motor activity measured in a modified Morris water maze.

Our findings are important for the genetic and neural basis of spatial learning in laboratory rodents.

Material and Methods

Animals and method of selection based on body mass

The experiment was conducted on male mice that originated from rodents selected from 94 generations at a lower level (L line, n=13) or high (H line, n=16) body mass at the time of weaning at 21st postnatal day (PND).

Differences in body weight between L and H lines were created by outbred stock constructed from the inbred strains: A/St, BN/a, BALB/c and C57BL/6J. There was no selection in the parallel running control line (Con, n=15). In the 94 generation of selection 30 females were monogamically mated within their lines (avoiding inbreeding). Pairs were kept together until two months after the last delivery or till the death of the partner. Offspring were reared with parents until weaning at 21st postnatal day (PND 21). From among them, forty four young males were chosen and housed 5–8 in plastic breeding cages in a temperature-controlled room (23°C) with a constant photoperiod (12 h : 12 h light/dark cycle) and air humidity 60–70%. Animals were given free access to tap water and standard granulated feed (Murigran) ad libitum. The body weight of animals were measured at 21, 56, 70, 90 and 100 postnatal day. The effect of selection based on body mass was conducted on mice in 100st PND and analyzed in the modified Morris water maze task. All procedures were carried out according to the regulations Ethical Committee for Animal Experiments at Agricultural University of Warsaw in compliance with the ethical standards of the European Communities Council Directive of 24 November 1986 (86/609/EEC).

Behavioral assessment

Water maze test

Mice were tested in the Morris water maze including acquisition trials and visual platform test (cued task) with minor modifications (WIDY-TYSZKIEWICZ et al. 1993). White, circular pool of 1.2 m diameter and 0.5 m deep was filed with water at 24±0.5°C. The experiment was performed during the light phase of the cycle (between 8.00–15.00 h). The pool was divided into four quadrants which were arbitrarily designed Northeast (NE), Northwest (NW), Southeast (SE) and Southwest (SW). The swimming pool was situated in the room with many objects that could be used by animals for spatial navigation. During training trials mice learned to escape from water by finding a submerged plexiglas platform (10 cm x 10 cm) hidden 0.5 cm below the water surface and placed in a fixed location in the center of SE quadrant. At the beginning of the

behavioral session each mouse was placed with its face toward the wall of the pool at one of three starting positions. During acquisition of the spatial navigation task mouse received 6 days of training with the hidden platform, each day included 4 training sessions (day 1–6; trial 1–24) with 15 s inter-session intervals. The starting location was diverse in each training trial and changed each day. The trial was terminated when the animal found the platform or until 60 s had elapsed. When the mouse found the platform it was allowed to remain there for 15 s. If the mouse didn't find the platform within this time it was placed on the platform by the experimenter for 15 s. At the end of day's session the mouse was removed from the pool, allowed to dry off and returned to its cage.

After completion of the hidden platform navigation task 24 h after last training trial, spatial memory was evaluated in the probe trial, on seventh day (day 7; trial 25). Memory test was performed after removing the platform and animals were allowed to swim for 60 s (probe trial).

Motor activity and motivation were evaluated in the cued task (day 8; trial 26–29). For the cued task the target platform was visible and placed 1 cm above the water line inside the pool. Data collection from Morris's water maze task that included escape latency, swim path length, swim speed, total time spend in the SE quadrant and the number of crossings over the former platform location, was automatically recorded using an HVS image analyzing system (Chromotrack, San Diego Instruments) and videotaping.

Statistical evaluation

Group differences were evaluated by applying analysis of variance – ANOVA with repeated measures (treatment × day × trial). Statistical analysis of the difference between groups was assessed with Student's t-test and two way ANOVA. Significant effects were further analyzed by post-hoc analyses (Newman-Keuls test and Student's *t*-test). All results are expressed as the mean ± SE for each experimental group. A value of $p<0.05$ was considered to be statistically significant.

Results

Body weight

Postnatal mean body mass of the light, heavy and control lines of mice are summarized in Table 1. Differences in the body mass between animals from the selected lines are presented on the 21st postnatal day (PND 21)

(Con: 13.35±0.13 g; L: 10.81±0.27 g; H: 14.42±0.17 g) ($F_{(2,41)}$=0.81) (p<0.001, Newman-Keuls) maintained at each time point where the body mass was measured (PND 56: $F_{(2,41)}$=1.58, p<0.001; PND 70: $F_{(2,41)}$=1.74, p<0.001; PND 90: $F_{(2,41)}$=1.68, p<0.001, Newman-Keuls). At 100st postnatal day, at the time of the behavioral experiment, the body mass of mice ranged between: 34.70±0.70 g for the control: 45.84±0.74 g for heavy line and 24.63±0.81 g for the low line and was significantly different between the control and experimental groups ($F_{(2,41)}$=2.11) (p<0.001, Newman-Keuls).

Table 1

Effect of divergent selection on the mean body mass (g ± SE) in light (L), heavy (H) and control (Con) line of mice on subsequent postnatal days (PNDs). ***L *vs* Con, p<0.001; $^{\#\#\#}$H *vs* Con, p<0.001; $^{\bullet\bullet\bullet}$L *vs* H, p<0.001 (Newman-Keuls test)

Mean body mass (g ± SE) in light, heavy and control line of mice on subsequent postnatal days					
Line	Postnatal day (PND)				
	PND 21	PND 56	PND 70	PND 90	PND 100
Light (L)	10.81±0.27$^{***\bullet\bullet\bullet}$	21.55±0.61$^{***\bullet\bullet\bullet}$	22.78±0.64$^{***\bullet\bullet\bullet}$	24.29±0.64$^{***\bullet\bullet\bullet}$	24.63±0.81$^{***\bullet\bullet\bullet}$
Heavy (H)	14.42±0.17$^{\#\#\#}$	40.25±0.97$^{\#\#\#}$	41.10±0.80$^{\#\#\#}$	44.41±0.91$^{\#\#\#}$	45.84±0.74$^{\#\#\#}$
Control (Con)	13.35±0.13	29.36±0.58	30.55±0.63	33.11±0.74	34.70±0.70

Behavior – water maze results

Acquisition trials (days 1-6; trials 1-24)

As shown in Fig. 1 the latency to escape to the platform in all groups of mice decreased following the training sessions. ANOVA for repeated measurements showed significant differences of place learning between the low and high body mass line ($F_{(2,41)}$=3.82, p<0.05, Newman-Keuls). The group with low body weight showed impairment of learning abilities compared to the high body mass line. Likewise significant effects in mean total escape latency for all experimental groups were found (Con: 40.75±0.90 s; L: 47.06±1.18 s; H: 36.17±1.11 s).

A statistically significant changes with considerable scatter of the results of latency were determined during all days of training. ANOVA analysis for a particular day of training and escape latency is as follows: Day 1: $F_{(2,173)}$=5.00, p<0.01; Day 2: $F_{(2,173)}$=6.16, p<0.001; Day 3: $F_{(2,173)}$=0.085, p>0.05; Day 4: $F_{(2,173)}$=3.69, p<0.05; Day 5: $F_{(2,173)}$=4.40, p<0.05; Day 6: $F_{(2,173)}$=4.38, p<0.05, Newman-Keuls.

As can be seen from Fig. 2 differences in total swim distance between all experimental groups (Con: 7.54±0.23 m; L: 8.33±0.26 m; H: 5.75±0.22 m;

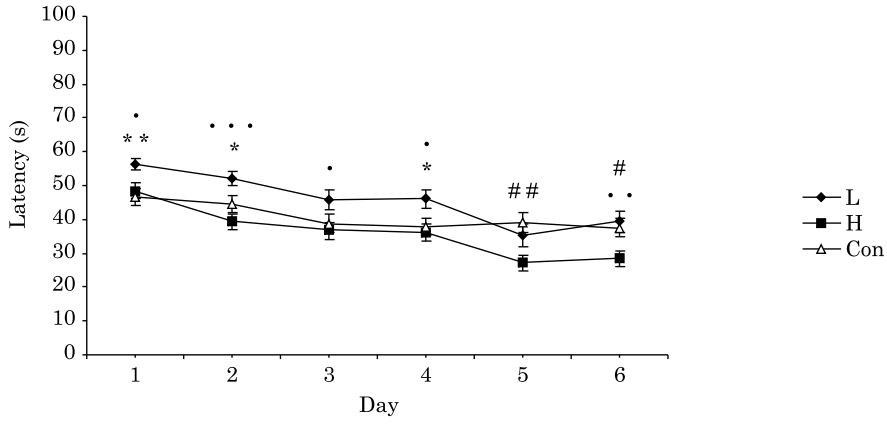

Fig. 1. Effect of divergent selection for body mass on spatial learning (time to escape from the water during acquisition trials using a submerged platform) in light (L), heavy (H) and control (Con) line of mice in the Morris water maze test. * L *vs* Con, $p<0.05$; ** L *vs* Con, $p<0.01$; $^{\#}$H *vs* Con, $p<0.05$; $^{\#\#}$H *vs* Con, $p<0.01$; •L *vs* H, $p<0.05$; ••L *vs* H, $p<0.01$; •••L *vs* H, $p<0.001$ (Newman-Keuls test)

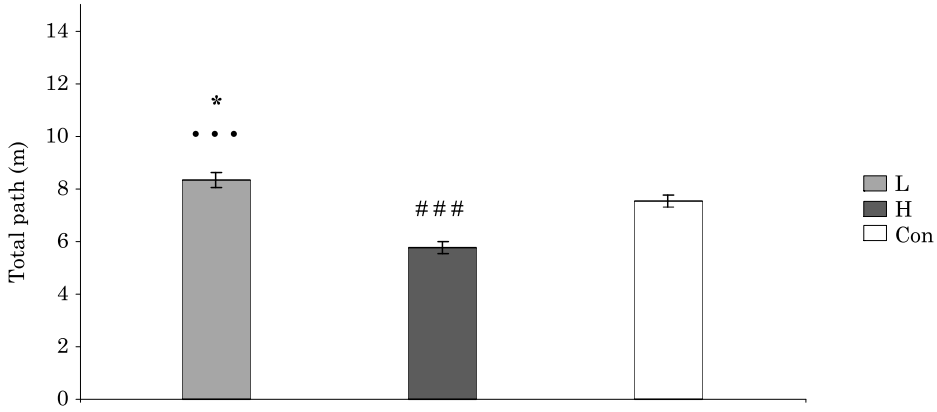

Fig. 2. Effect of divergent selection for body mass on mean swim distance during acquisition trials in light (L), heavy (H) and control (Con) line of mice in the Morris water maze test. * L *vs* Con, $p<0.05$; $^{\#\#\#}$H *vs* Con, $p<0.001$; •••L *vs* H, $p<0.001$ (Newman-Keuls test)

$F_{(2,1053)}=31.77$; $p<0.001$) have been found. The Newman-Keuls test also confirms the differences in swimming speed between the mice from heavy line, light line and the control group (Con: 0.19±0.003 m/s; L: 0.19±0.003 m/s; H: 0.17±0.04 m/s; $F_{(2,1053)}=18.34$; $p<0.001$, Newman-Keuls) (Fig. 3).

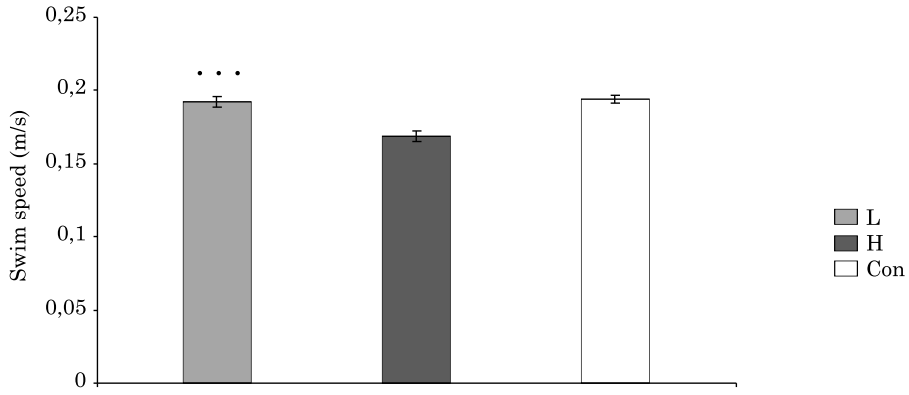

Fig. 3. Effect of divergent selection for body mass on mean swim speed during acquisition trials in light (L), heavy (H) and control (Con) line of mice in the Morris water maze test. •••L *vs* H, $p<0.001$ (Newman-Keuls test)

The probe trial-memory test (day 7; trial 25)

Platform crossings on the previous SE position did not show significant effects following line selection ($F_{(2,41)}=0.58$; $p>0.05$, Newman-Keuls). The time spent in target quadrant SE (earlier platform's position) did not differ between groups ($F_{(2,41)}=0.29$; $p>0.05$, Newman-Keuls). There wasn't any significant difference between groups in the percentage of time spent in the remaining quadrants (SW: $F_{(2,41)}=1.80$; NW: $F_{(2,41)}=0.26$; NE: $F_{(2,41)}=1.88$; $p>0.05$, Newman-Keuls). No significant effects in total swim distance ($F_{(2,41)}=2.18$) and speed ($F_{(2,41)}=2.24$; $p>0.05$, Newman-Keuls) for all experimental groups were found.

Visible platform test (day 8; trials 26–29)

An analysis of variance did not demonstrate significant difference between groups in the mean escape latency in the cued task on Day 8 ($F_{(2,173)}=1.51$; $p>0.05$). However we have seen an extended search time for the visible platform in the group of mice with the low body weight (47.60±3.00 s) compared to the heavy line (34.92±2.95 s) and the control (41.40±2.69 s). Results of the cued task on day 8 indicate an increase in the mean swimming speed in light line. The average swimming speed was lower in heavy line (0.12±0.007 m/s) and in the control group (0.16±0.012 m/s) *vs* light line (0.27±0.058 m/s) ($F_{(2,173)}=5.35$; $p<0.01$). The results did not show a significant main effect for mean distance travelled ($F_{(2,173)}=0.45$; $p>0.64$).

Discussion

In the present work we have demonstrated the consequences of multigenerational selection for the low or high body mass on spatial learning, memory, motivation and motor abilities in mice.

The body mass is a polygenic simple measured quantitative trait with moderate to high heritability. The present experiment demonstrates that multigenerational selection based on body weight results in the significant modulation of behavior with subtle changes concerning spatial learning in mice. Mice from two selected lines differ in body mass at the weaning and through the whole lifespan. The statistical analysis shows significant differences between the groups in the acquisition in the water maze test.

Our observations are partially compatible with the results of other investigators. Similar conclusions were reached by Padeh and Soller (1976), who found a positive genetic correlation between body mass in inbred strains of mice and T-maze learning ability as well as the relationship between body mass, cerebrum weight and learning evaluated in this assay. Numerous studies have documented that spatial memory depends on the combination of several genetic and environmental factors which contribute to spatial learning ability and cognition. One of the relevant factors which may be important for the proper functioning of the central nervous system and cognitive processes is the nutritional status (ACHAM et al. 2008).

In our experiment the ability of spatial learning in mice from heavy line evaluated in water maze was found to be increased. We notice frequently the restriction of the early postnatal development due to the large size of the litter in rodents. Based on observations made by the team of Jou and co-authors (2013) we can infer that, as in our experiment, early postnatal growth retardation leads to poorer developmental outcome and worse learning behavior.

Certain studies involving laboratory animals suggest that dietary restriction particularly early in life will not only reduce the incidence of genetic diseases and pathological changes, but also prolongs the mean life span (LLOYD 1984, MASORO 2000, WEINDRUCH 1996). Mice from the light line lived longer than rodents with high body mass (heavy line) (WIRTH-DZIECIOŁOWSKA and CZUMIŃSKA 2000). Results presented by Takahashi et al. (2006) suggested that the food reduction initiated at an early stage of life improves the acquisition of the passive avoidance task in animal model of accelerated aging. This beneficial effect in terms of memory improvement in mice scientists linked with changes in neuronal functions rather than with histological alteration in the brain (TAKAHASHI et al. 2006). Similarly, recent studies indicated that manipulation of caloric content produces learning and memory deficits in this distinctive strain of mice (KOMATSU et al. 2008).

A very interesting and intriguing conclusions were made by Cunnane and Crawford (2003) who developed theories that „fat babies were the key to evolution of the large human brain". According to this hypothesis, fetal fat deposits are required for the proper functioning of the developing brain and constitute the key to the evolution of the mammalian central nervous system.

On the other hand scientific evidence suggests that obesity may cause brain dysfunction (NILSSON and NILSSON 2009), changes in personality traits and anatomical variations in the brain structures in humans e.g. as increasing gray matter volume in the hippocampus (MORENO-LÓPEZ et al. 2012). It was also shown that a high body mass index (BMI) is correlated with decreased gray matter volume in the orbitofrontal regions and lower cognitive functioning (WALTHER et al. 2010). Interestingly, high BMI resulted in faster visuomotor speed. Study by GUNSTAD et al. (2007) based on studies involving 408 healthy subjects demonstrated that elevated BMI is negatively correlated with cognitive performance and other executive functions observed in overweight and obese adults. Poorer neurocognitive outcome was probably associated with a number of pathophysiological amendments within the cardiovascular system and impaired insulin regulation.

Integrative analysis of genetic factors related to complex traits such as body weight and obesity is extremely difficult. One of the technique that enables understanding the molecular mechanism and genetic basis of these complex traits is a module-guided Random Forest (mgRF). Many genes identified by this method may potentially contribute to the variation of the mouse body mass e.g. Mogat1, Cyp2c37, Gpld1 (CHEN and ZHANG 2013). Other studies analyzing the genetic basis of response to multi-generational selection on body weight in inbred mice were conducted by Keightley and Hill in 1989. In their experiment the high and low lines of mice derived from a subline of the inbred strain C3H/He were used. The authors emphasize the earlier observation of the increase of genetic variance of quantitative traits due to the accumulation of new mutations which may in turn be responsible for the artificial selection. At the same time, these studies suggest that between 38 and 50 generations a plateau, manifested in a little subsequent selection response is reached. Under the experimental conditions, selection can determine the extent of the inheritance of the complex quantitative traits and predict consequences of long-term selection for some characteristics in future. However, depending on the time scale, the effect and final goals of selection may vary. Long-term experiments may be useful for evaluating changes in response rates or differences caused by selection and provide details about the underlying inheritance of quantitative traits.

It should be noted that the lines of mice used in the experiment were created by outbred stock constructed from few inbred strains (A/St, BN/a,

BALB/c and C57BL/6J), which differ not only in the phenotypic traits but also in the neuroanatomical features, sensory and behavioral abilities (BROWN and WONG 2007). NGUYEN et al. (2000) indicated the existence of the strain-dependent variations in hippocampal long-term potentiation and spatial memory in inbred mice. Characteristic memory deficits in the Morris water maze were found in CBA/J mice, whereas both in DBA/2J and CBA/J strains impaired nonspatial learning and long-term memory in the contextual and cued fear conditioning tests were observed. As demonstrated *in vitro*, abnormalities in cognitive abilities in DBA/2 strain can be partly explained by reduction of the paired-pulse facilitation – the early phase of LTP in CA1 area of the hippocampus.

Even though, there was no line specific differences in the cued task, it is well known that mice with poor vision like BALB/c exhibited poor performance in the tests requiring distal location e.g. in radial arm maze (BROWN and WONG 2007).

It is reasonable to assume the existence of a connection between body size, longevity, diet and environmental factors, increased selective pressure for mental/social adaptation and behavioral innovation which eventually results in the increased brain size (WARD et al. 2004).

The relative brain weight (brain/body weight ratio) is considered to be one of the most important indicators of the evolutionary level of species. In the vertebrates, the brain size is affected and shaped by many factors operating separately. Despite the fact that having a larger brain (relative to body size) brings many benefits, the energy cost of maintaining this organ is very high and not always justified by evolution (FITZPATRICK et al. 2012, ROTH and DICKE 2005).

It is not exactly known which of the features: size of the brain, degree of encephalization or structural and functional specialization of cerebral cortex, most accurately reflects the animal intelligence (DEANER et al. 2007). However, previous studies show clearly and unequivocally the empirical link between brain size and mental and behavioral flexibility in primates (READER and LALAND 2002). Analysis of 100 postmortem human brains demonstrates that visuospatial skills and verbal intelligence is positively related to cerebral volume (WITELSON et al. 2006).

Jacobs and co-authors (1990) demonstrated that the evolution of spatial cognition and hippocampal size shows some differences based on gender. Moreover, behavioral differences between monogamous and polygamous laboratory strains of mice with larger hippocampus in the males have been shown. Another series of studies on the effect of selection for the body weight reported differences in the growth and changes occurring with age between the heavy and light lines. Analysis of differences in the longevity and aging of mice from

body weight selected lines show earlier mortality in the males from heavy line. This effect in this group was correlated with earlier weight loss and higher hyperplasia of the cortex cells in adrenals.. Selection for body weight induced also differences in exploratory behavior in mice measured in the open field and Lashley maze (WIRTH-DZIECIOŁOWSKA et al. 2005). The line with low body mass showed higher anxiety and impairment of spatial learning.

Salimov and co-authors (2004) pointed out that mice lines selected for different brain weight exhibit pronounced diversity in exploratory behavior and fear tendencies. The differences are particularly apparent with regard to the fear-anxiety and spontaneous stereotypic behavior. Mice with larger brain weight show higher scores of locomotion in peripheral parts of the open field arena, more rearing and less frequent freezing and grooming compared to the mice with smaller brain. Hybrid F2 mice with larger brain weight moved faster and more likely demonstrated stereotyped behavior in the cross-maze test (SALIMOV et al. 2004). Not unlikely, that it is related to higher sensitivity or increased response to the pain stimuli presented by those with lower brain weight. This proven relationship between phenotypes of the selected lines of mice and their behavior is a very interesting problem, but previous research has displayed divergent experimental data (FALCONER 1953, FOWLER 1962, HOLMES and HASTIGS 1995).

Body weight is a multigenic conditioning trait additively affected by genes, therefore simple divergent selection may easy lead to changes in the other features. Long-term selection for body composition produced significant differences in the proportion of gonadal fat and total body fat in the *Fat* and *Lean* lines of mice (MARTINEZ et al. 2000). These observations are confirmed by the results carried out by Eisen and co-authors (1978, 1987, 1988), which shows the particular relationship between the body weight and weights of the perigonadal fat.

The cumulative data indicate the occurrence of correlations of body weight with ovulation rate, mortality and embryo number, placental and fetuses weight and other reproduction traits. Selection of mice for the body weight for over 90 generations resulted in a differentiation in their sexual maturation rate. Determinations of the level of sexual hormones and histology of gonads confirm that mice from line L reached maturity later compared to the animals from H line. Changes in the weight of parovarian fat in females show clear connection with the period of reaching sexual maturity and length of the reproductive time (WIRTH-DZIĘCIOŁOWSKA et al. 1996). Evaluation of differences in the morphological structure and function of ovaries and testes in mice from line selected divergently for body weight show that degeneration of testicular stroma and inhibition of spermatogenesis were more advanced in mice from the light line. The divergent selection for body weight in rabbits

leads to the reduction of the semitendinosus muscle weight and decrease of the diameter of the constitutive myofibers in the low body weight line (LARZUL et al. 2005).

The results presented here lead to the conclusion that selection of mice for high and low body mass over 94 generations resulted in a differentiation of their cognitive abilities.

To sum up, long-term selection for body mass results in the changes in many behavioral traits including spatial learning and motor activity. There was a decrease in the ability to learn Water Maze test in mice from a light line. In the future, it will be necessary to perform profound analysis of the genetic background of the observed changes in the behavior and the identification of the molecular and cellular substrates of place learning in the selected lines of mice.

The observed differences in learning ability in the selected lines can generate practical consequences both for breeders and researchers.

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