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Intermale Aggression in Laboratory Mice, Selected for the Cognitive Trait

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Abstract

Aggression level of male mice EX, which belonged to line, selected for the high scores of cognitive test solution [ability to extrapolate the direction of food bait movement after it disappears from animal view] was compared to that of male mice from control unselected population CoEX. The standard opponent test was used. At the start of selection [F5] EX mice were more aggressive, while at F10-15 the pattern of differences changed and CoEX mice were significantly more aggressive. These data could be partly explained by differences between EX and CoEX in their anxiety and reaction to novelty.

Highlights: Selection for cognitive trait induced changes in the intermale aggression

Intermale aggression is presumably related to anxiety level

Less aggressive mice are not afraid of novel food

Keywords: Intermale Aggression; Cognitive Abilities; Artificial Selection; Anxiety; Novelty; Mice

Introduction

Directed aggression is considered to be the important component in mammal species specific behavior [1], the expression of this behavior reveals the variability of both - genetic and environmental origin [2- 5]. Animal aggression is studied not only for elucidating its biological roots but also for creating the adequate models which would help to investigate the mechanisms of human aggression which is inherent in many psychiatric disorders. Aggression phenotype is heterogeneous and differs by function and motivation [6-9]. The important fraction of studies in animal aggression field are those, performed using laboratory rodents, when aggression is investigated in its relation to anxiety and reactions to stressors [10, 11], and to cognitive behavior as well [12- 14]. These issues are difficult to analyze both because of different techniques used by authors and also due to the complicated nature of animal anxiety [15, 16]. Differences in stress-reactions, induced as the result of intermale conflicts, were of opposite sign in two groups when animals of selected lines were used. In LAL-SAL mouse lines [selected for short- and long attack latencies on the basis of wild mouse population] the stress reactivity was lower in more aggressive SAL mice. At the same time the stress reactivity was higher in low anxiety and more aggressive [LAB] rats in comparison to HAB [High anxiety] rats [HAB-LAB lines were selected for differences in anxiety in elevated plus maze test]. In another selection experiment anxiety indices were higher in non-aggressive mice when TA-TNA selected mice [Turku Aggressive и Turky Non-Aggressive] were compared [17], and this difference was confirmed by pharmacological experiments. Mice of North Carolina lines [NC-900 и NC-100, selected for different aggression levels] differed by their reactivity in response to environmental factors, and aggressive NC-900 mice were more reactive. The anxiety level in NC-900 was also higher, the fact, which don't correspond the data on other selected mouse lines. The comparison of Roman high- and low avoidance rats [RHA-RLA], selected for fast and slow active avoidance acquisition demonstrated higher activity and lower aggression in fast learning RHA rats, while RLA animals which acquired avoidance habit more slowly, were more anxious and tended to freeze [18].

The data obtained demonstrated, that in rodents, selected for different levels of aggressiveness, the respective phenotypic correlations [i.e. the plausible correspondence of aggressiveness, anxiety and general reactivity levels] are only partly based on common physiological mechanisms. The same seems to be true when animals, selected for other behavioral traits, were compared. No clear correlations could be seen as well when aggression levels are compared with cognitive tests performance [19]. Although the knocking out of one BDNF allele, or the forebrain-restricted deletion of both these alleles in mice induced not only increased aggression but also the increase in anxiety and deficits in cognition. Thus, rather complicated pattern of correlations between aggression and other behavioral traits emerges, presumably due to [i] heterogeneity of aggression traits as different aggressive genotypes could be created in technically different selection experiments, while the "aggressive" traits in selected lines look rather similar by their phenotype [20,21] and [ii] the heterogeneity of anxiety phenotypes. The complexity of genetic bases of cognitive traits could make its own impact in the complicated patterns of phenotype correlations discovered.

The objective of the present work was to determine the intermale aggression level [in standard opponent test] in EX mice, i.e. line selected for high scores of elementary logic task solution [extrapolation test], in comparison to these indices in

control unselected mice - population CoEX [22-24]. The data from elevated plus maze test [as anxiety indices] for EX and CoEX mice are also presented which were obtained previously during several selection generations [starting from F4]. Light-dark box test data for mice of both groups from F16 are also included.

Material and Methods

Experimental animals. The intermale aggression test was performed in total with 130 EX and CoEX male mice [age 6-7 months] from 4 generations of this selection [F5, F10, F12, and F15]. EX line mice were selected from the genetically heterogenous population [22] for high scores of extrapolation task - the ability to extrapolate the direction of food bait movement which disappears from animal view. In short: animal approaches the opening in the frontal wall of the box and thus have the short access to the bait [a cup of milk] via this opening; after several seconds the cup moves to the left or to the right [in quasi-random order] and disappears from animal's view; in order to get the food the mouse has now to move in the direction of food bait movement and approach the respective side opening [in front of which the cup is now placed – the correct choice]; the movement in the opposite direction and nose-poke into the empty side opening was the incorrect choice [25].

The animals which were chosen for breeding in each generation [for EX strain] should conform two criteria – i] the animal should display the correct solution of extrapolation task at its first presentation [when an animal had no previous analogous experience] and demonstrate the 5-6 correct solutions during 6 subsequent task presentations and ii] apart from extrapolation test success they should reveal no "refusals to solve the task", when the mouse did not approach the central feeding opening during 3 min [arbitrary interval]. Such refusals are the distinct signs of anxiety, aroused in animal by the new environment, as well as the cases when the solution took more than 120 s [also arbitrary chosen interval].

The behavior of EX mice in all tests was compared with that of mice from the unselected population [CoEX], which were bred in parallel with EX line. The numbers of mice tested in dyadic encounters are presented in table 1.

Table 1: The aggressive behavior scores in EX and CoEX male mice (m ± s.e.) in successive generations of selection for high scores of cognitive trait (n - number of animals)

Generation	Trait	First attack latency, seconds			Number of Attacks		
	Days of Test	1	2	3	1	2	3
F5	EX n=8	**606.3±122.6***	**608.6±139.8***	**421.3±122.4****	5.0±1.6	**11.8±2.7****	**10.1±2.4***
	CoEX n=8	1113.8±122.6	1069.7±139	1082.7±121.6	1.8±1.5	1.5±2.7	1.4±2.3
F10	EX n=20	**1171.3±66.9*****	**1096.9±66.5*****	**1051.8±98.7****	**0.4±0.3***5**	**1.5 ±0.7****	**1.3±0.7***
	CoEX C n=19	782.4±68.6	623.8±68.2	556.4±101.2	6.7±1.8	9.3±2.9	8.9±2.9
F12	EX n=19	**1200±65.6****	**1149.9±70.5***	**1147.8±85.9***	**0***	**0.3±0.7***	**0.4±0.8***
	CoEX n=20	913.7±63.9	902.4±68.7	860.4±83.7	1.8±0.5*	2.5±0.7	2.8±0.8
F15	EX n=18	**1178.1±48.9****	**1131.1±66.0***	**1094.9±73.5****	0.1±0.8	**0.7±1.2***	3.1±2.2
	CoEX n=18	960.3±48.9	923.8±66.0	791.7±73.5	2.7±0.8	4.8±1.2	6.7±2.2

*, **, *** - significantly different from scores for CoEX mice, p<0.05, 0.01 and 0.001, respectively (1 factor ANOVA, Tukey HSD test)

Non-aggressive males of A/Sn strain [and in the part of experiments – males from C57BL/6J x 129/J hybrid population] were used as "standard opponents".

All animals were kept in plastic cages [26.7 x 20.7 x 14 cm] with natural light-dark schedule and food [Chara firm] and water ad lib. The experimental procedures were performed in accordance with ES 2010 Directive.

Standard opponent test procedure. Before the start of tests on intermale aggression EX and CoEX males were kept isolated in individual cages [26.7 x 20.7 x 14 cm] in mouse colony room for 10 days.

At the start of the test two males [experimental one and the "standard opponent"] were placed simultaneously in the plastic cage [42.5 x 26.6 x 15 cm] with fresh bedding [wood shaving] and were watched for 20 min. Latency of the first attack, total number of attacks, the number of aggressive "forced" grooming and tail rattling episodes as well as sniffing of the partner [data not presented] were manually recorded. The proportions of animals from each group which demonstrated the directed aggression toward the rival were also estimated. When animal aggression was scored relying on the data from the single encounter there is the risk to get the biased data due to chance variability [26]. Thus the repetitive testing was performed - each pair of males was tested during three successive days.

Light-dark box [LDB] test was performed with F16 males from EX [n=16] and CoEX [n=18] groups [in F15 there were not enough animals to form the groups for this test]. LDB was the opaque plastic box divided by partition in two unequal parts – the dark one [15, 5 x 29,5 x 28 cm] and brightly lit [58 x 29,5 x 28 cm]. The partition contained the opening [5,5 x 4,5 cm] for an animal to pass through. Animal was placed into the brightly lit

compartment and the latency of the first entrance into the dark was manually recorded. The time spent in the dark, number of returns into the lit compartment, numbers of peeping reactions in and out the dark compartment and defecation boli numbers were also recorded.

Elevated plus maze test [EPM]. The data on EPM performance in EX and CoEX mice were partly described previously [22-24]. During 3 min test the number of animal's entries into the open EPM arms, time spent there, closed arm-closed arm transitions, hangings from open arms, stretched-attend postures, as well as the number of rearings, grooming episodes and defecation boli were manually registered. This test was presented to males of F4, F6, F8, F9, F10, F12, F16 [n=175 in total for EX and n=178 - for CoEX mice, see (Table 2).

Table 2: Behavior of EX and CoEX mice from different selection generations in the EPM test (m ± s.e.) (n- number of animals).

Generation	Group	Time in open arms, secc	Entries into open arms	Closedarm-closed arm transitions	Number of grooming episodes
F4	EX n=16	**51.3±6.1****	4.5±0.5	2.4±0.8	1.88±0.3
	CoEX n=12	30.4±7.3	2.92±0.6	4.08±0.8	2.4±0.77
F6	EX n=36	**29.8±3.4***	**3.08±0.3***	**2.4±0.36***	**1.36±0.2*****
	CoEX n=32	14.2±2.3	1.44±0.26	1.09±0.28	4.06±0.4
F8	EX n=14	12.2±1.6	1.78±0.28	**5.6±0.9***	1.9±0.32
	CoEX n=14	19.0±4.1	1.78±0.4	**2.9±0.7**	1.6±0.26
F9	EX n=25	8.7±1.7	0.64±0.2	2.4±0.5	**2.88±0.4***
	CoEX n=17	8.9±1.9	0.76±0.2	2.5±0.6	1.59±0.3
F10	EX C n=34	**8.0±1.4***	0.56±0.15	1.2±0.3	**2.65±0.26***
	CoEX n=53	6.6±0.8	0.25±0.08	2.0±0.37	1.8±0.18
F12	EX n=34	5.9±1.0	0.3±0.1	1.0±0.2	**2.7±0.2*****
	CoEX n=36	7.4±1.2	0.38±0.1	1.36±0.29	1.5±0.18
F16	EX n=16	0.3±0.4	**0.18±0.06***	2.6±0.4	0.9±0.3
	CoEX n=14	0	0	1.9±0.4	0.85±0.3

*, **, *** - significantly different from scores for CoEX mice, p<0.05, 0.01 and 0.001, respectively, 1-factor ANOVA, Tukey HSD test)

Statistics. One-factor ANOVA was used to evaluate the EX-CoEX differences in aggression and anxiety experiments [Statistica 6] with post hoc Tukey HSD test. The differences in proportions of mice from two mouse groups which demonstrated aggression were evaluated using Fisher φ test.

Results

The highly aggressive and non-aggressive mice were found in both EX and CoEX groups, although their numbers and respective proportions differed in different selection generations.

All mice from the "standard opponent" group, when not attacked by rivals, demonstrated "neutral" behavior. They emitted no overt reactions when they were olfactory investigated by the rival, they never initiated the contacts and conflicts and they started to freeze for long periods and to avoid the rival after being attacked [data not presented].

The results of aggressive encounters [attack latencies, number of attacks] are presented in the (table 1). F5 EX males demonstrated higher aggression than CoEX mice. This statement is based on several experimental evidences - first attack latencies of EX's were significantly shorter and the attack numbers during each day of tests – higher, than in CoEX mice [table 1], and the proportion of animals, which demonstrated aggression towards the opponent, was also significantly higher in EX, than in CoEX.

In F10, F12 и F15 the "sign" of intergroup differences changed into the opposite one – the aggression level in EX males was now lower than in CoEX. This difference concerns not only the intergroup comparison, but is seen in absolute trait magnitudes as well - the proportion of aggressive CoEX males in F5 was 12%, while in F15 – it was significantly higher - 67% [p<0.01].

It should be noted that the behavior of animals during dyadic encounters also changed in the course of selection. In F5 the attacks of EX mice were longer in duration [>20 s] and very intense, while later, in F10 their attacks were sparse, although still of rather long duration. At the same time EX males from F12 and F15 revealed the tendency to avoid the opponent and demonstrated the overt fear reactions. They tended to stay in the cage corners and did not enter the center of this arena. As for CoEX males the picture was the reverse – in F5 their attacks were rare and short [<5 s], while in F10 both these indices increased and remained at rather high levels in F12 and F15. The proportions of CoEX aggressive mice in these generations were also high (Figure1).

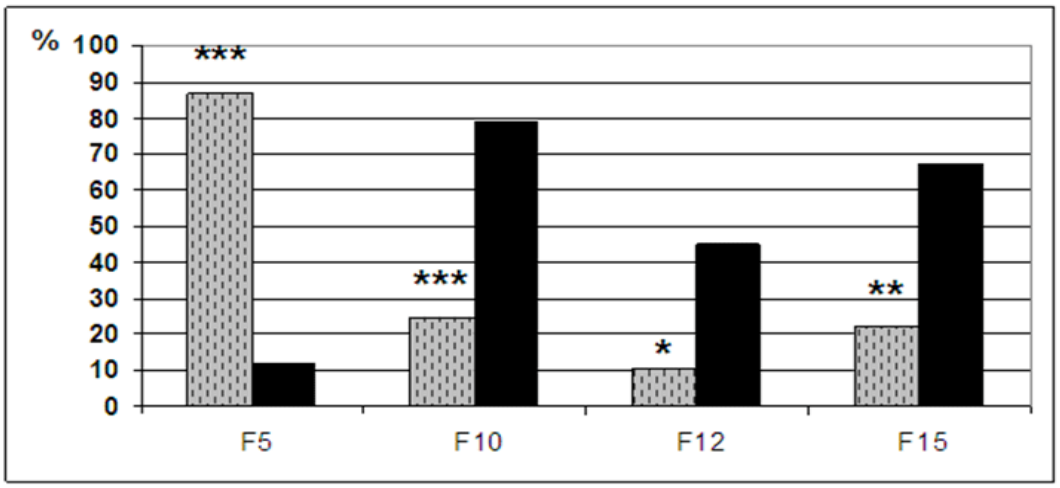

Figure 1: The proportions (%) of EX (grey columns) and CoEX (black columns) mice, which demonstrated aggression in standard opponent test during selection for high scores of the cognitive trait*, **, *** - significantly different from the respective proportion of CoEX mice ($p<0.05$, 0.01 and 0.001, respectively, φ Fisher test)

The data on forced grooming of the opponent and on tail rattling episodes are presented in fig.2 and fig 3, respectively. These behaviors are usually regarded as being connected with the aggressive motivation of not high intensity, although these behaviors could indicate the presence of the conflict between aggressive motivation and fear experienced by a subject [27-29].

The pattern of EX - CoEX differences in scores of these reactions in the course of selection were of the same type as for attack latencies and numbers, although these grooming episodes [but not tail rattlings] numbers were more or less equal in F15 mice of both groups. (Figure 2, 3)

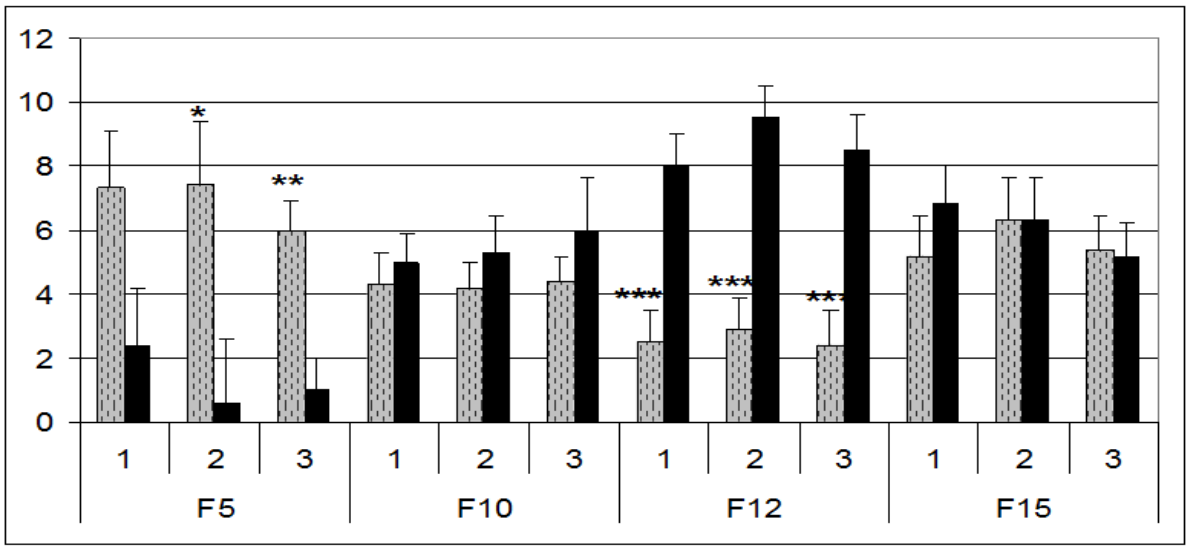

Figure 2: Numbers (mean ± s.e.) of forced grooming episodes in EX and CoEX mice during standard opponent tests in different selection generations. *, **, *** - significantly different from CoEX scores (1-factor ANOVA and post hoc Tukey HSD test). Designations as in Fig.1

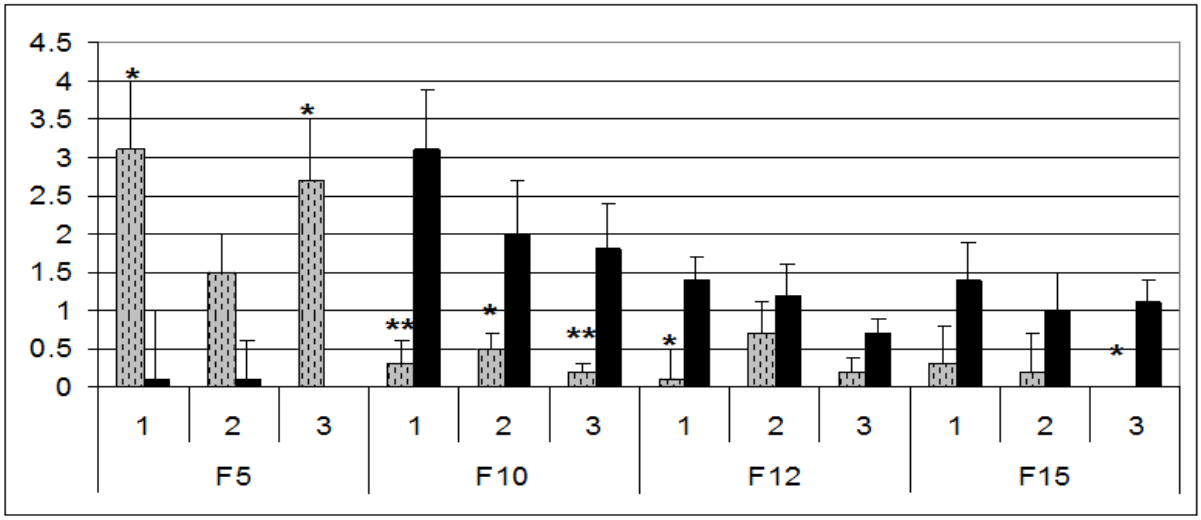

Figure 3: Numbers of tail rattling episodes in EX and CoEX mice in selection generations. *, **, *** - significantly different from CoEX scores (1-factor ANOVA and post hoc Tukey HSD test). Designations as in Fig.1

The pattern of differences between EX and CoEX mice in EPM test indices also changed as the selection experiment proceeded. The time spent in open arms and number of entries into these parts of EPM [the "reverse" anxiety indices], as well as self-grooming episodes were higher in F4 - F8 EX mice. Although, starting from F9 these differences were no longer so systematic (Table 2). In other words the lower anxiety level in EX mice [revealed earlier in EPM test in comparison with CoEX] was not their stable characteristic anymore in further selection generations.

The anxiety indices of LDB test, performed by F16 mice, demonstrated that time in dark compartment was significantly [$p<0.05$] longer in EX mice [92.13±11,3 s] in comparison with CoEX [61.55±9.4 s], and this could signify the higher level of their overall anxiety.

Discussion

The data presented in this paper evidence that the "sign" of differences in aggression scores between EX and CoEX mice changed from F5 to later generations [table 1]. It should be mentioned that the selection of mice for high scores of extrapolation task performance was performed with concomitant selection against anxiety and fear expression during this test (see Introduction and 25, 22,24) [22,24,25]. The "refusals to solve the task" was taken as an index of animal fear towards the extrapolation test environment. These "refusals" were the cases when an animal does not approach the central feeding opening [which is the starting point of test procedure], and thus don't drink milk from a cup. It is obvious that the refusal to contact of the opening prevents an animal from the possibility to get the food in case of correct solution, although such "refusals" occurred not in all task presentations during experiment, but these animals were excluded from the further reproduction. Initially these "refusals" [which were selected against] became significantly less frequent in EX mice in comparison with these indices in the initial population and in CoEX mice [22,25]. This means that during initial selection generations the response to selection against fear and anxiety [aroused in animals placed in the new environment] was evident. Anxiety indices of EPM test in early selection generations were also lower in EX mice [table 2]. In F4 and F6 the time, spent in open arms by EX mice, was about two times higher than that for CoEX [23]. Note, that aggression in F5 EX males was higher than in CoEX mice. Although in later generations [starting from F8] EX-CoEX differences in EPM scores became unstable. Although the numbers of "refusals" to perform the extrapolation task did not decrease significantly over these generations [data not presented]. In other words we were not able to detect the stable lower level of anxiety in mice of the selected line [and it was even non-significantly higher in F8, F11 and F12]. At the same time the neophagophobia test [reaction to the new food in the new environment] revealed the significant differences in EX and CoEX behavior in F8 - F11 with EX mice revealing lower phobia of the novelty [23]. It should be reminded that in these generations EX mice were significantly less aggressive, than CoEX.

In the neophagophobia test, when the new food was presented to hungry animal in the new [although not provoking avoidance] environment, the anxiety displayed by an animal, is of the type not identical to anxiety displayed in EPM. In other words the signs of anxiety behavior in the hyponeophagophobia test were consistently lower in EX mice in the same generations in which EPM test revealed no such differences [23]. Several authors [15,16,30] also suggest that the anxiety of the type which reflects the species specific fear of open and brightly lit space [displayed in EPM, LDB and open field tests] is not identical to the state of anxiety-alertness, which animals [including rodents] display in the new environment [i.e., in neophagophobia test]. Our data on EPM [starting from F8] and on LDB [F16] tests indicated the

higher "overall" species-specific anxiety in EX mice. And up to the present moment there are no obvious explanations of the dynamic changes of this type of anxiety during selection generations.

The pattern of differences which was shown in this study resemble the correspondence of aggression and general anxiety in SAL-LAL and TA-TNA lines [see above], i.e. in lines which were directly selected for aggression traits. The non-aggressive lines in these pairs of lines demonstrated higher anxiety.

Unfortunately the neophagophobia test was not presented to mice of early generations. Starting from F8 the differences in these indices [23] made it possible to suggest that EX mice were more prone to overcome the specific fear of the new environment, than CoEX control mice.

The neophagophobia test results are usually not easy to interpret, as an animal could reveal both - the positive reaction to novelty as well as the fear of it [31]. This means that animal ability to suppress the fear of new environment [which is not the "full developed" species-specific anxiety] was more clearly expressed in EX mice. Although it should be reminded, that EX mice were less aggressive in the late selection generations. At the same time "reaction to novelty" could be considered as the component of the cognitive behavior [23].

Our selection experiment did not result in clear increase of extrapolation task scores [which were selected for], although the success of EX mice in another cognitive test - the burrowing [puzzle-box] task - was noted in comparison with CoEX animals [24]. These results permit to cautiously suggest, that the prevalence of EX mice scores in burrowing task is the response to selection for cognitive trait. It is also possible that the cognitive component of neophagophobia test performance in EX corresponds their ability to overcome the fear of novelty in puzzle-box, and this ability was less evident in CoEX mice [23-24].

Many experimental evidences indicated the role which brain neurotransmitter systems play in determination of aggression level [8]. At the same time the increased anxiety is associated with the serotonergic system hypofunction [5,33,34]The involvement of noradrenergic and glutamatergic systems in the realization of aggressive behavior was also shown [11,35,36]. The genetic studies permitted to localize the set of genes involved in the expression of this behavior [14,37,26,38] The switch-off of genes, participating several signaling pathways, was shown to increase the intermale aggression as well [3,13,35] The interstrain differences in lines, selected for high and low cholinergic system reactivity [Flinders lines], also affected the aggression traits [4], which could be also the evidence of genetic modulation of the aggression level.

The experimental data on intermale aggression in mice, which were selected for cognitive trait, could be regarded as the so called correlated trait, and this in turn means that genetic variability has the impact in this trait expression. The selection for the cognitive trait was successful during initial selection generations [23], although this selection gain was not maintained during further selection. The same pattern was noted for the selection against anxiety behavior, which mice displayed in the new environment [i.e. against "refusals" to solve the task]. No marked differences were noted in this trait in the later selection generations [in comparison to CoEX]. The results of this study permit us to state the following. These traits [anxiety in the new environment and logic task solution ability] have rather complicated genetic basis, but the anxiety, displayed in the EPM test and in the course of extrapolation test are not similar, i.e. the anxiety is not a "uniform" state. In other words we suggest that the notion "anxiety" encompasses: first, the state of general fear-anxiety which is developed in the uncomfortable frightening environment [open-field, EPM and LDB], and second, the anxiety state, which is aroused when animal faces the need to explore the "novelty" when no real overt danger is present and the environment is more or less "comfortable". This view coincides with opinion developed by other authors [39].

Analyzing the complicated pattern of EX-CoEX behavioral differences one more consideration is also worth mentioning. It could be that the integrated adaptive behavior of an animal [i.e. displayed during rather complicated logic task as that of extrapolation] requires the definite level of anxiety to be expressed in the behavioral repertoire of an animal [may be even anxieties of both types, hypothesized above]. The decrease of anxiety during artificial selection procedure could evoke the compensatory shifts which would counteract such selection effects. Thus one may suggest that changes in EX mice aggression levels in response to selection for high cognitive test scores with the concomitant selection against anxiety signs are the result of complex changes in mouse adaptive behavior.

Conclusion

The selection of laboratory mice for high level of capacity to solve the elementary logic task [ability to extrapolate the direction of stimulus, disappeared from view] resulted in the increase of the solutions success but not in the extrapolation ability but in ability to solve the "puzzle-box" burrowing task. The intermale aggression level in EX mice, described in this study, was higher, than in controls, in F5 of selection experiment, but lower in F10-15. The animals with higher general [EPM tested] anxiety were less aggressive, the fact which suggest the complicated relationships of these traits.

References

1. Blanchard R.J, Blanchard D C. Attack and defense in rodents as etho-experimental models for the study of emotion. Prog Neuropsycho-pharmacol Biol Psychiatry. 1989; 13 Suppl: S3-14.
2. Nehrenberg DL, Rodriguiz RM, Cyrd M, Zhange X, Lauder JM, Gariupy JL, Wetsel WC. An anxiety-like phenotype in mice selectively bred for aggression. Behav Brain Res. 2009; 201(1): 179-191. DOI: 10.1016/j.bbr.2009.02.010.
3. Veenema AH, Neumann ID. Neurobiological mechanisms of aggression and stress coping: a comparative study in mouse and rat selection lines. Brain Behav Evol. 2007; 70(4): 274-285. DOI: 10.1159/000105491.

4. Pucilowski O, Eichelman B, Overstreet DH, Rezvani AH, Janowsky DS. Enhanced affective aggression in genetically bred hypercholinergic rats. Neuropsychobiology. 1990-1991; 24(1): 37-41. DOI: 10.1159/000119040.
5. Ferrari P F, Palanza P, Parmigiani S, de Almeida RMM, Miczek KA. Serotonin and aggressive behavior in rodents and nonhuman primates: Predispositions and plasticity. Eur. J. Pharmacol. 2005; 526: 259–273. DOI: 10.1016/j.ejphar.2005.10.002.
6. Parmigiani S, Ferrari PF, Palanza P. An evolutionary approach to behavioral pharmacology: using drugs to understand proximate and ultimate mechanisms of different forms of aggression in mice. Neurosci Biobehav Rev. 1998; 23(2): 143-153.
7. Sluyter F, Korte MS, Bohus B, Van Oortmerssen GA. Behavioral stress response of genetically selected aggressive and nonaggressive wild house mice in the shock-probe/defensive burying test. Pharmacol Biochem Behav. 1996; 54(1): 113-116.
8. Miczek KA, Fish EW, De Bold JF, De Almeida RM. Social and neural determinants of aggressive behavior: pharmacotherapeutic targets at serotonin, dopamine and gamma-aminobutyric acid systems. Psychopharmacology (Berl). 2002; 163(3-4): 434-458. DOI: 10.1007/s00213-002-1139-6
9. Blanchard DC, Griebelc G, Blanchard R J. Conditioning and residual emotionality effects of predator stimuli: some reflections on stress and emotion. Prog Neuropsychopharmacol Biol Psychiatry. 2003; 27(8): 1177-1185. DOI:10.1016/j.pnpbp.2003.09.012.
10. Hogg S, Hof M, Würbel H, Steimer T, de Ruiter A, Koolhaas J, Sluyter F. Behavioral profiles of genetically selected aggressive and nonaggressive male wild house mice in two anxiety tests. Behav Genet. 2000; 30(6): 439-446.
11. Vekovischeva OY, Aitta-aho T, Verbitskaya E, Sandnabba K, Korpi ER. Acute effects of AMPA-type glutamate receptor antagonists on intermale social behavior in two mouse lines bidirectionally selected for offensive aggression. Pharmacol Biochem Behav. 2007; 87(2): 241-249. DOI: 10.1016/j.pbb.2007.04.020.
12. Ouchi H, Ono K, Murakami Y, Matsumoto K. Social isolation induces deficit of latent learning performance in mice: a putative animal model of attention deficit/hyperactivity disorder. Behav Brain Res. 2013; 238: 146-153. DOI: 10.1016/j.bbr.2012.10.029.
13. Ito W, Chehab M, Thakur S, Li J, Morozo A. BDNF restricted knockout mice as an animal model for aggression. Genes Brain Behav. 2011; 10(3): 365-374. DOI: 10.1111/j.1601-183X.2010.00676.x.
14. Sala M, Braida D, Lentini D, Busnelli M, Bulgheroni E, Capurro V, Finardi A, et al. Pharmacologic rescue of impaired cognitive flexibility, social deficits, increased aggression, and seizure susceptibility in oxytocin receptor null mice: a neurobehavioral model of autism. Biol Psychiatry. 2011; 69(9): 875-882. DOI: 10.1016/j.biopsych.2010.12.022.
15. Cryan JF, Sweeney FF. The age of anxiety: role of animal models of anxiolytic action in drug discovery. Br J Pharmacol. 2011; 164(4): 1129–1161. DOI: 10.1111/j.1476-5381.2011.01362.x.
16. Ennaceur A. Tests of unconditioned anxiety - pitfalls and disappointments. Physiol. Behav. 2014; 135: 55-71. DOI: 10.1016/j.physbeh.2014.05.032.
17. Nyberg JM, Vekovischeva O, Sandnabba NK. Anxiety profiles of mice selectively bred for intermale aggression. Behav Genet. 2003; 33: 503-511.
18. Coppens CM, de Boer SF, Steimer T, Koolhaas JM. Correlated behavioral traits in rats of the Roman selection lines. Behav. 2013; Genet. 43, 220–226.
19. Kazlauckas V, Schuh J, Dall'Igna OP, Pereira GS, Bonanc CD, Lara DR. Behavioral and cognitive profile of mice with high and low exploratory phenotypes. Behav. Brain Res. 2005; 162: 272–278. DOI : 10.1016/j.bbr.2005.03.021.
20. Sandnabba NK. Predatory aggression in male mice selectively bred for isolation-induced intermale aggression. Behav Genet. 1995; 25(4): 361-366.
21. Tulogdi A, Toth M, Halasz J, Mikics E, Fuzesi T, Halle J. Brain mechanisms involved in predatory aggression are activated in a laboratory model of violent intra-specific aggression. Eur J Neurosci. 2010; 32(10): 1744-1753. DOI: 10.1111/j.1460-9568.2010.07429.x.
22. Perepelkina OV, Markina NV, Golubrodo VA, Lilp IG, Poletaeva II. Selection of mice for high level of extrapolation task solution with concomitant selection for low level of anxiety. J. of Higher Nervous Activity by I.P. Pavlov.61, 742-749.
23. Perepelkina OV, Golibrodo VA, Lilp IG, Poletaeva II. Selection of laboratory mice for the high scores of logic task solutions: the correlated changes in behavior. Adv Biosci Biotechn. 2014; 5: 294-300. DOI: 10.4236/abb.2014.54036.
24. Perepelkina OV, Golibrodo VA, Lilp IG, Poletaeva II. Selection of mice for high scores of elementary logical task solution. Advances in Bioscience and Biotechnology. 2014; 5: 294-300.
25. Poletaeva II, Zorina ZA. Genetic Approach to the Study of Simple Cognitive Abilities in Animals. The Rus. J. Cogn. Sci. 2014; 1: 31-55.
26. Dow C, Kreibich AS, Kaercher KA, Sankoorikal GMV, Pauley E D, Lohoff FW, et al.. Genetic dissection of intermale aggressive behavior in BALB/cJ and A/J mice. Genes, Brain and Behav. 2011; 10(1): 57–68. DOI: 10.1111/j.1601-183X.2010.00640.x.
27. Mondragón R, Mayagoitia L, López-Luján A, Díaz JL. Social structure features in three inbred strains of mice, C57Bl/6J, Balb/cj, and NIH: a comparative study. Behav Neural Biol. 1987; 47(3): 384-391.
28. Russell JW, Greenberg BD, Segal DS. The effects of phencyclidine on spontaneous aggressive behavior in the rat. Biol Psychiatry. 1984; 19(2): 195-202.
29. Aureli F, Yates K. Distress prevention by grooming others in crested black macaques. Biol Lett. 2010; 6(1): 27-29. DOI: 10.1098/rsbl.2009.0513.
30. Salomons A R, Arndt SS, Ohl, F. Impact of anxiety profiles on cognitive performance in BALB/c and 129P2 mice. Cogn Affect Behav Neurosci. 2012; 12(4): 794-803. DOI: 10.3758/s13415-012-0109-7.

31. Rob MJ Deacon. Hyponeophagia: a measure of anxiety in the mouse. J Vis Exp. 2011; (51): 2613. DOI: 10.3791/2613
32. Gordon G, Fonio E, Ahissar E. Emergent exploration via novelty management. J Neurosci. 2014; 34(38): 12646-12661 DOI: 10.1523/JNEUROSCI.1872-14.2014.
33. Popova NK, Nikulina EM, Kulikov AV. Genetic analysis of different kinds of aggressive behavior. Behav. Genet. 1993; 23: 491-497.
34. De Boer SF, Koolhaas JM. 5 -HT1A and 5-HT1B receptor agonists and aggression: A pharmacological .challenge of the serotonin deficiency hypothesis. Eur. J. Pharm. 2005; 526: 125–139.
35. Sallinen J, Haapalinna A, Viitamaa T, Kobilka BK, Scheinin M. Adrenergic alpha2C-receptors modulate the acoustic startle reflex, prepulse inhibition, and aggression in mice. J Neurosci.1998; 18(8): 3035-3042.
36. Caramaschi D, de Boer SF, Koolhaas JM. Is hyper-aggressiveness associated with physiological hypoarousal? A comparative study on mouse lines selected for high and low aggressiveness. Physiol Behav. 2008; 95(4): 591-598. DOI:10.1016/j.physbeh.2008.08.019.
37. Selmanoff MK, Maxson SC, Ginsburg BE. Chromosomal determinants of intermale aggressive behavior in inbred mice. Behav. Genet.1976; 6: 53-69.
38. Malki K, Pain O, Du Rietz E, Tosto MG, Paya-Cano J, Sandnabba K N, et al. Genes and gene networks implicated in aggression related behaviour. Neurogenetics. 2014; 15(4): 255-266. DOI: 10.1007/s10048-014-0417-x.
39. Ennaceur A, Michalikova S, Chazot PL. Do rats really express neophobia towards novel objects? Experimental evidence from exposure to novelty and to an object recognition task in an open space and an enclosed space. Behav Brain Res. 2009; 197; 417-434. DOI: 10.1016/j.bbr.2008.10.007.