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ORIGINAL ARTICLE

FEATURES OF BLOOD PARAMETERS AND ADAPTATIONAL STATUS OF BALB/C AND C57BL/6 MICE LINES IN THE ABSENCE OF SPECIAL INFLUENCES

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ABSTRACT

Purpose of the study. A comparative analysis of blood parameters and some characteristics of the adaptation status of intact Balb/c and C57Bl/6 mice of both sexes.

Materials and methods. We investigated intact mice of both sexes belonging to the C57Bl/6 (*n* = 18) and Balb/c (*n* = 20) lines. The age characteristics of these animals corresponded to the first half of the reproductive period. We studied the parameters of the complete and biochemical blood tests, the weight characteristics of the thymus, spleen and adrenal glands. The character and tension of general nonspecific adaptational reactions of the body (AR) were assessed as well. In statistical analysis we used the coefficient of variation (CV), Student's t-test, Mann-Whitney test.

Results. In mice of both studied lines, the dominance of females over males was noted in terms of the weight characteristics of the thymus and spleen, the development of the most favorable antistress AR, and the number of indicators with low variability. At the same time, in C57Bl/6 mice, animals of different sexes had a similar nature of AR (AR of elevated activation), but differed in signs of tension, this might indicate the difference in the range of levels of reactivity, appropriate to AR in males and females C57Bl/6. Unlike C57Bl/6, mice Balb/c mice of different sexes were distinguished with the predominant antistress AR. Differences between C57Bl/6 mice and Balb/c mice in terms of amylase and ALT activity indicated a shift towards carbohydrate metabolism in Balb/c mice and a shift towards protein metabolism in C57Bl/6 mice. Animals of the C57Bl/6 line had an advantage over Balb/c mice (especially pronounced in females) in some indicators of the adaptation status.

Conclusion. The results of the study indicated possible difference in the ratio of carbohydrate and protein metabolism in the animals of the studied lines and testified a more favorable state of the regulatory systems in C57Bl/6 mice compared to animals of the Balb/c line. The revealed regulatory and metabolic interlinear differences can determine the features in the reaction of the body of animals belonging to different lines to the malignant process and efficiency of antitumor therapy.

Keywords: hematological parameters, adaptation status, antistress adaptational reactions, metabolism

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Compliance with ethical standards: work with animals was carried out in accordance with the rules of the «European Convention for the Protection of Animals Used for Experimental and other Scientific Purposes» (Directive 2010/63/EU), as well as in compliance with the «International Recommendations for Biomedical Research Using Animals» and Order of the Ministry of Health of Russia No. 267 of June 19, 2003 «On Approval of the Rules of Laboratory Practice». The study was approved by the Ethics Committee of the National Medical Research Centre for Oncology (Protocol No. 11/115 of 03/01/2021).

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ОРИГИНАЛЬНАЯ СТАТЬЯ

ОСОБЕННОСТИ ПОКАЗАТЕЛЕЙ КРОВИ И АДАПТАЦИОННОГО СТАТУСА МЫШЕЙ ЛИНИЙ BALB/C И C57BL/6 ПРИ ОТСУТСТВИИ СПЕЦИАЛЬНЫХ ВОЗДЕЙСТВИЙ

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РЕЗЮМЕ

Цель исследования. Сравнительный анализ показателей крови и некоторых характеристик адаптационного статуса интактных мышей линий Balb/c и C57Bl/6 обоего пола.

Материалы и методы. Исследования проводили у интактных мышей обоего пола линий C57Bl/6 (*n* = 18) и Balb/c (*n* = 20). Возрастные характеристики животных соответствовали первой половине репродуктивного периода. Изучали показатели общего и биохимического анализа крови, весовые характеристики тимуса, селезенки и надпочечников. Оценивали характер и напряженность общих неспецифических адаптационных реакций организма (АР). При статистическом анализе использовали коэффициент вариации (CV), t-критерий Стьюдента, критерий Манна-Уитни.

Результаты. У мышей обеих изученных линий было отмечено доминирование самок над самцами по весовым характеристикам тимуса и селезенки и частоте развития наиболее благоприятной антистрессорной АР повышенной активации. Вариабельность изученных показателей в целом у самок была ниже, чем у самцов. При этом у мышей линии C57Bl/6 животные разного пола имели сходный характер АР (АР повышенной активации), но отличались признаками напряженности этой реакции, указывающими на разный диапазон уровней реактивности, на которых развивалась эта АР у самцов и самок. У мышей линии Balb/c животные разного пола различались характером преобладавших антистрессорных АР. Сравнение биохимических показателей крови самок разных линий указывало на более активный углеводный обмен у мышей линии Balb/c и более активный белковый обмена – у мышей линии C57Bl/6. Животные линии C57Bl/6 имели преимущество над мышами Balb/c (особенно выраженное у самок) по некоторым показателям адаптационного статуса.

Заключение. Результаты исследования указывали на возможное различие в соотношении углеводного и белкового обмена у самок Balb/c и C57Bl/6 и свидетельствовали о более благоприятном состоянии регуляторных систем у мышей линии C57Bl/6 по сравнению с животными линии Balb/c. Выявленные регуляторные и метаболические межлинейные различия могут обусловить особенности в реакции организма животных, принадлежащих к разным линиям, на злокачественный процесс и эффективность противоопухолевой терапии.

Ключевые слова: гематологические показатели, адаптационный статус, антистрессорные адаптационные реакции, метаболизм

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INTRODUCTION

Research on animal models is aimed at identifying the fundamental mechanisms of carcinogenesis and experimental substantiation of new drugs and methods of treatment. At the same time, there is a need to identify and separate universal patterns and features of tumor and organism reactions due to molecular genetic characteristics, the state of regulatory systems of specific individuals [1; 2], sex [3–5] and age of animals [6; 7], their linear affiliation [5; 8]. Mice of the Balb/c and C57Bl/6 lines are among the laboratory rodents most widely used in biomedical research, including preclinical trials of new drugs and technologies for antitumor treatment [1; 9]. There is information about several anatomical, reproductive and behavioral features of these animals that need to be taken into account when conducting experimental studies [10–12]. At the same time, the question of interlinear differences in the functioning of their regulatory systems and adaptive status remains little studied, which, considering the different stress resistance of these animals [1; 13; 14] and their highly probable origin from different subspecies of mice Mus musculus [15; 16], seems very important in the development of effective methods of antitumor effects and the identification of universal pathogenetically significant processes. The relevance of this issue is enhanced due to the rather long existence of the experimental animal lines under consideration, since an increase in the number of closely related crosses could lead to an increase or, conversely, to a weakening of the previously known immunological and physiological characteristics of mice of these lines [15].

The informative value of biochemical and cytological indicators of blood for the general assessment of the state of the body, as well as the correlation of the adaptive status with the processes in the organs of the immune and neuroendocrine systems [17; 18] allows the use of hematological indicators and shifts in the weight characteristics of internal organs to objectify the results of studies and identify universal systemic rearrangements under the action of damaging factors. One of the stages of solving these problems is a comparative analysis of indicators reflecting the state of regulatory systems, the adaptive status and features of the metabolism of animals of these lines in the conditions of the physiological norm.

Purpose of the study was the comparative analysis of blood parameters and some characteristics of the adaptive status of intact Balb/c and C57Bl/6 mice of both sexes.

MATERIALS AND METHODS

The parameters characterizing the condition of intact mice of both sexes belonging to the C57 Black/6 (n = 18) and Balb/c (n = 20) lines were studied. We used animals of our own breeding vivarium of NMRC for Oncology, Russian Ministry of Health, originally purchased from the Rappolovo nursery. Each of the four groups (control and main groups of animals of the two studied lines) included 9–10 animals. Their age characteristics corresponded to the first half of the reproductive period. According to the known dependencies between weight and life expectancy of laboratory rodents of various lines [9; 19] the age of mice of the C57Bl/6 line was 9–12 weeks, and in mice of the Balb/c line this indicator corresponded to 9–16 weeks. The differences in life expectancy were random in nature, were due to the limited choice of mice with matching weight characteristics, the possibilities of their own breeding, and were not critical of their belonging to the category of young animals capable of intensive reproduction [9].

To assess the features of the general condition and adaptive status of intact animals of different lines, a study of the complete blood count test (CBC) and biochemical blood analysis, as well as the weight characteristics of the thymus, spleen and adrenal glands (weight and weight coefficients of these organs) was carried out. At the same time, special attention was paid to the percentage of lymphocytes in the blood, the mass and weight coefficients of the thymus and adrenal glands, as well as to the ratio of the masses of these organs as indicators of the nature and intensity of the general nonspecific adaptive reactions of the AP organism [17; 18]. Necropsy, isolation and weighing of organs of animals subjected to euthanasia by decapitation were performed. The weight coefficient of the organ was the ratio of the mass of the organ to the mass of the animal in grams multiplied by 10^4. To determine the blood parameters obtained after euthanasia, the Exigo EOS vet hemoanalyzer (Boule Medical A. B., Sweden) and the VetScanVS2 biochemical analyzer (ABAXIS Inc., Germany) were

used. At the same time, in the case of C57Bl/6 mice, biochemical blood parameters were determined only in females (due to technical difficulties that prevented the determination of these indicators in males). Statistical processing of the results of the study was carried out using the software package Statistica 10.0. The range of variations of the studied indicators, their medians, averages and errors of averages, as well as the coefficient of variation (CV) were determined. The Student's t-test (with a normal distribution of indicator values) and the nonparametric Mann-Whitney test were used to evaluate statistical differences in the variation series.

STUDY RESULTS

As a result of a comparative analysis of the studied hematological parameters, weight characteristics of the immune system and adrenal glands, as well as the ratio of thymus and adrenal mass in animals of both sexes, the peculiarities of the nature and severity of sexual differences, as well as several interlinear differences in the value of individual indicators in mice of the same sex were revealed. Table 1 shows the indicators that had sex differences in the animals of the studied lines.

Earlier we've discussed sex differences in cytological and biochemical blood parameters and weight characteristics of the internal organs of the immune system and adrenal glands of intact Balb/c mice [20] (Table 1). In these animals, with close values of hemoglobin levels in the blood, there were sex differences in the number of red blood cells and their saturation with hemoglobin. At the level of the weight characteristics of the studied organs, the differences between female mice and male mice of this line consisted in a slightly more active proliferation in the thymus (revealed by the weight of the organ, taking into account the slightly larger age of female mice than males), noticeably larger adrenal glands (which was a well-known constitutional feature of female mice of the Balb/c line) [1] and the spleen (Table 1). These differences, along with the distinctive features of blood biochemical parameters and a noticeably higher percentage of lymphocytes, allowed us to make an assumption about a more pronounced activation of the T-cell link of immunity and a higher adaptive status of females, the development of AR increased activation in them. As is known, it is this AR that is distinguished by the most noticeable increase in the activity of regulatory systems and the level of nonspecific resistance of the body [18]. At the same time, the combination of signs observed in male mice could indicate the development of AR training and quiet activation [2; 18] and a relatively higher activity of the B-cell link and neutrophils compared to that observed in females (a shift of the albumin-globulin index towards globulins, higher than in females, the activity of alkaline phosphatase, capable of influencing the state of B-lymphocytes and neutrophils) [21; 22].

As can be seen from Table 1, in mice of the C57Bl/6 line, similar to that noted for animals of the Balb/c line, there were sexual differences in the weight coefficient of the spleen and adrenal glands, as well as in the saturation of erythrocytes with hemoglobin. The relative weight of the spleen of female mice of both lines was at least 1.5 times higher than this indicator in males, while the differences in the other two indicators had the opposite direction. Thus, females of the Balb/c line differed from males by larger adrenal glands (a well-known constitutional feature of these animals) [1] and a lower average hemoglobin level in the erythrocyte. In contrast, in female mice of the C57Bl/6 line, the relative weight of the adrenal glands was lower, and the saturation of erythrocytes with hemoglobin was slightly higher than in males (Table 1).

In addition, male mice of the C57Bl/6 line differed from females with a higher platelet count and larger adrenal glands. At the same time, the weight coefficients of the thymus and the ratio of the mass of the thymus and adrenal glands of females significantly exceeded these indicators in males (1.9 and 2.8 times, respectively), while the percentage of lymphocytes in both cases corresponded to the maximum values of the reference interval for this line and had no sex differences (Table 1). Thus, in animals of the C57Bl/6 line, the dominance of females over males in terms of thymus weight characteristics was expressed more clearly than in mice of the Balb/c line, which could reflect a higher level of lymphoproliferative activity in the thymus of females.

Table 2 shows the indicators that differ in male mice of the studied lines. Males of C57Bl/6 were superior to same-sex mice of the Balb/c lineage in terms of adrenal gland weight, leukocyte level and percentage of lymphocytes in the blood. The

Table 1. Blood counts and weight characteristics of internal organs that differ in mice of the C57Bl/6 and Balb/c line of different sexes. ($X_{av.}$ ± *m*, *Me* [X_{min} – X_{max}], CV %)

Parameter		Male	Female
C57Bl/6	Thymus weight	35.2 ± 5.7 32 [23–59] 32.5 % *n* = 9	56.2 ± 7.7^{T} p = 0.064 58 [41–79] 27.3 % *n* = 9
	Thymus weight coefficient	14.4 ± 2.4 13.1 [9.6–19.6] 33 %	27.6 ± 3.4* *p* = 0.016 27.3 [20–38.5]* *p* < 0.01 24.9 %
	Adrenal glands weight	18.1 ± 1.1 17 [16–21] 12.4 %	10.5 ± 0.7* *p* = 0.00006 11 [8.5–12]* *p* < 0.01 12.6 %
	Adrenal glands weight coefficient	7.5 ± 0.8 6.9 [5.9–9.5] 21.0 %	5.2 ± 0.2* *p* < 0.001 5 [4.6–5.8]* *p* < 0.01 8.8 %
	Spleen weight	81.6 ± 4.0 80 [71–91] 9.8 %	102.4 ± 7.1* *p* = 0.038 99 [88–126]* *p* < 0.05 14.3 %
	Spleen weight coefficient	33.4 ± 2.2 32.3 [27.8–38.3] 12.9 %	51.3 ± 6.4* *p* = 0.03 46.8 [42.9–74.1]* *p* < 0.01 25.1 %
	Thymus mass/adrenals mass	1.9 ± 0.4 1.6 [1–3.1] 42.8 %	5.4 ± 0.55* *p* < 0.001 5.1 [4.8–7.2]* *p* < 0.01 20.6 %
	Mean Corpuscular Hemoglobin (pg)	17 ± 0.3 16.8 [16.6–17.9] 3.2 %	18.6 ± 0.4* *p* = 0.015 18.5 [17.3–19.7]* *p* = 0.01 4.7 %
	Platelets' count. (10^9/л)	994 ± 18.5 1006 [943–1030] 3.7 %	735 ± 77.5* *p* = 0.014 755 [515–905]* *p* < 0.01 21.1 %
Balb/c	Thymus weight	28.4 ± 5.3 30 [13–42] 37.3 % *n* = 10	4.1 ± 5.7^{T} *p* = 0.098 43 [24–68] 35.7 % *n* = 10
	Thymus weight coefficient	10.1 ± 1.6 9.1 [5.8–14.2] 32.8 %	13.3 ± 2.1 13.2 [8.5–24.7] 41.7 %
	Adrenal glands weight	14.2 ± 1.7 15 [10–19] 24.1 %	28.9 ± 1.9* *p* = 0.00003 28 [21–32]* *p* < 0.01 18.4 %
	Adrenal glands weight coefficient	5.1 ± 0.23 5.1 [4.4–5.9] 13.5 %	9.0 ± 0.6* *p* = 0.00003 8.3 [7.6–11.8]* *p* < 0.01 16.8 %
	Spleen weight	84.2 ± 14 94 [39.4 – 130] 50.0 %	156 ± 5.0* *p* = 0.0002 154 [131–179]* *p* < 0.01 9.5 %
	Spleen weight coefficient	29.4 ± 4.0 36.9 [14.3–39.3] 40.8 %	48.8 ± 1.9* *p* = 0.00003 49.7 [39.7–54.2]* *p* < 0.01 10.3 %
	Erythrocyte count (10^9/л)	5.57 ± 0.42 5.8 [3.9–6.4] 22.6 %	6.9 ± 0.42* *p* = 0.042 7.3 [3.8–8.2]**p* < 0.01 18.4 %
	Mean Corpuscular Hemoglobin (pg)	21.8 ± 0.8 21.4 [19.9–25.2] 11.0 %	19.5 ± 0.7* *p* = 0.048 18.8 [17.5–25.5]* *p* < 0.01 11.2 %
	Lymphocytes, %	69.6 ± 4.0 71.4 [49.4–84.7] 17.2 %	83.6 ± 1.33* *p* = 0.0050 84.2 [77.4–87.7]* *p* < 0.01 5.0 %
	Monocytes, %	13.3 ± 1.7 12.9 [6.5–20.5] 38.3 %	7.24 ± 0.50* *p* = 0.0041 7.0 [5.4–10.2]* *p* < 0.01 20.6 %

Note: * – it is statistically significantly different from the indicators in male mice; ^{T} – is the difference from the indicator in male mice at the tendency-like levels (*p* < 0.1).

hemoglobin content in the red blood cells of males C57Bl/6 was less significant compared to Balb/c males and was compensated by a higher number of red blood cells in the blood of these animals, which caused a tendency to a higher hemoglobin level in these animals compared to Balb/c males (Table 2).

Attention was drawn to the lower variability of a number of indicators in males of the C57Bl/6 line compared with Balb/c mice of the same sex. Thus, all three characteristics of the erythrocyte blood germ and the relative content of lymphocytes in males C57Bl/6 had CV values below 10 %. At the same time, the percentage of lymphocytes in these animals, similar to that noted earlier for Balb/c females [20], was practically constant (CV % = 2.2 %, Table. 2), was in the range of the maximum values of this indicator in animals of the considered line [10] (Table. 2) and could indicate the development of AR increased activation in these males [18].

Data on the interline differences in the indicators of female mice of the studied lines are presented in Table 3. It should be noted that in females these differences were expressed to a greater extent than in males. Thus, female C57Bl/6 mice were distinguished by a significantly larger thymus and significantly smaller adrenal glands than Balb/c females. As a result, the ratio of thymus and adrenal gland mass in C57Bl/6 females was 3.4 times higher than this indicator in Balb/c female mice (Table 3).

In addition, in C57Bl/6 females, significantly higher values were also noted for such indicators as the level of leukocytes in the blood, as well as the activity of the enzymes alanine aminotransferase (ALT) and alkaline phosphatase (1.4 and 2.7 times, respectively). At the same time, the indicator of amylase activity in the blood of these animals was almost 2 times lower than in female mice of the Balb/c line (Table 3). The interlinear differences in the activity of amylase and ALT could indicate the distinctive

Table 2. The studied indicators differ in male mice of the lines C57Black/6 and Balb/c. ($X_{av.} \pm m$, *Me* [$X_{min} – X_{max}$], CV %)

Parameters	Balb/c, *n* = 10	C57Bl/6, *n* = 9
Adrenal glands weight coefficient	5.1 ± 0.34 5.1 [4.4–5.9] 13.4 %	7.5 ± 0.8* *p* = 0.0280 6.9 [5.9–9.5]* *p* < 0.01 21.0 %
Blood hemoglobin levels (g/L)	119.7 ± 6.8 120 [89–138] 13.9 %	135.2 ± 3.3^{T} *p* < 0.07 136 [128–143] 4.9 %
Erythrocyte count (10^9/L)	5.57 ± 0.42 5.8 [3.9–6.4] 18.4 %	7.9 ± 0.3* *p* = 0.0014 8.2 [7.2–8.5]* *p* < 0.01 6.9 %
Mean corpuscular hemoglobin (pg)	21.8 ± 0.8 21.4 [19.9–25.2] 8.6 %	17 ± 0.3* *p* = 0.00033 16.8 [16.6–17.9]* *p* < 0.01 3.2 %
Leukocyte count (10^9/L)	4.8 ± 0.5 5.3 [3–6] 27.6 %	10.7 ± 1.0* *p* = 0.0005 10.8 [8.2–12.2]* *p* < 0.01 18.5 %
Relative lymphocyte count, %	69.6 ± 4.8 71.4 [49.4–84.7] 17 %	85.8 ± 1.0* *p* = 0.0092 86.3 [83–87.8]* *p* < 0.01 2.2 %
Relative monocyte count, %	13.3 ± 2.02 12.9 [6.5–20.5] 37.3 %	6.5 ± 0.4* *p* = 0.0092 6.2 [5.8–7.6]* *p* < 0.01 12.5 %

Note: * – statistically significantly differs from the indicators in male mice of the Balb/c line; ^{T} – differs from the indicators in male mice of the Balb/c line at the trend level, $p < 0.1$.

features of metabolism in Balb/c and C57Bl/6 mice – a higher level of carbohydrate metabolism in female Balb/c mice and a shift towards protein metabolism in C57Bl/6 animals.

In female mice of the studied lines, stable (CV 3.1 and 5.0 %, respectively, in animals of the C57Bl/6 and Balb/c lines) values close to the maximum and almost identical values of the percentage of lymphocytes in the blood (84.0 and 83.6 %, respectively) were observed, which could indicate the development of AR in these animals increased activation [2; 18]. At the same time, as in the case of comparing males of different lines, attention was drawn, in general, to the lower variability of indicators in animals of the C57Bl/6 line (Table 3). Thus, in the females of this line, the CV values of adaptive status indicators did not exceed 25 %, whereas in the same–sex mice of the Balb/c line with them, 3 of the 7 indicators presented in Table 3 differed in high variability (CV 41.7–56 %).

DISCUSSION

As it is known, the adaptive status of humans and animals can be assessed by determining the nature and intensity of AR, which have an integral character and reflect the state of the regulatory systems of the body [2; 17; 18]. The percentage of lymphocytes in the blood, the weight coefficients of the organs of the immune and endocrine systems, the ratio of the masses of the thymus and adrenal glands allowed us to give an approximate assessment of the adaptive status of the animals of the studied lines. The maximum for this line and stable values of the percentage of lymphocytes in C57Bl/6 mice (CV 2.2 and 3.1 %, respectively, in males and females) indicated the development of AR increased activation in animals of both sexes. At the same time, a significantly larger thymus in females and at the same time noticeably smaller adrenal glands compared to these indicators in males could indicate a higher level of reactivity

Table 3. The studied indicators, differing in female mice C57Bl/6 and Balb/c. ($X_{av.}$ ± *m*, *Me* [X_{min} – X_{max}], CV %)

Parameters	Balb/c, *n* = 10	C57Bl/6, *n* = 9
Thymus Weight Coeficient	13.3 ± 2.1 13.2 [8.5–24.7] 41.7 %	27.6 ± 3.4* *p* = 0.016 27.3 [20–38.5]* *p* < 0.01 24.9 %
Adrenals Weight Coeficient	9.0 ± 0.6 8.3 [7.6–11.8] 18 %	5.2 ± 0.2* *p* = 0.001 5.0 [4.6–5.8]* *p* < 0.01 8.8 %
Thymus Weight / Adrenals Weight	1.6 ± 0.3 1.6 [0.6–3.2] 56 %	5.4 ± 0.55* *p* = 0.000016 5.1 [4.8–7.2]* *p* < 0.01 20.6 %
Leukocyte count (10^9/L)	3.8 ± 0.54 3.35 [1.8–7] 42.6 %	10.3 ± 1.1* *p* = 0.000071 10.5 [7.6–13]* *p* < 0.01 22.4 %
Alkaline phosphatase	53.44 ± 2.63 55 [47 – 61] 13.9 %	104 ± 11* *p* = 0.00095 100 [83–123]* *p* < 0.01 21.2 %
ALT	31.8 ± 2.3 32 [21 – 44] 20.6 %	46.4 ± 3.8* *p* = 0.0072 49 [38–56]* *p* < 0.01 16.6 %
Amilase	1124 ± 72 1098 [875–1502] 19 %	586 ± 33* *p* = 0.00003 606 [495–662]* *p* < 0.01 11 %

Note: * – statistically and significantly differs from the indicators in male mice.

compared to males, at which AR increased activation developed in females of the C57Bl/6 line [2; 18]. As is known, the concept of the level of AR reactivity is associated with the previously identified periodic pattern of the development of these reactions, which consists in the dependence of the nature and intensity of AR on the absolute and relative magnitude of the effect causing them [18]. It has been shown that as the intensity of the active factor increases or decreases, the AR tetrads (AR of training – AR of calm activation – AR of increased activation – AR stress) naturally repeat. At the same time, the same-named ARS of different levels of reactivity caused by effects of different intensity, along with similar features (percentage of lymphocytes, ratio of effects of gluco- and mineralcoticoid hormones, etc.), have differences in the severity of signs of tension in the functioning of the regulatory systems of the body. At the same time, the most physiological antistress AR, which most contribute to the activation of systemic mechanisms of nonspecific resistance, develop in response to low-intensity effects of various nature, that is, at high levels of reactivity of the body.

The lower levels of reactivity at which AR increased activation developed in males of the C57Bl/6 line, compared with the reactivity levels of the same AR in females, could be due to the psychosomatic state formed in males upon reaching puberty and causing their aggressive behavior. As is known, this behavior is accompanied by activation of ergotropic processes, an increase in the level of catecholamines and testosterone in blood and tissues, as well as a more significant level of cellular energy [23; 24].

As previously described, Balb/c mice showed sex differences in the percentage of lymphocytes and some other indicators [20]. Based on the totality of these changes, it was possible to judge the sexual differences in the adaptive status associated with the nature of AR – the development of AR increased activation in females and the development of AR training and quiet activation, including signs of tension of these AR – in males. As already mentioned earlier, such differences in the nature of AR in animals of different sexes could be due to the dependence of the psychosomatic state of males on their social status in the group, and could also reflect the presence of any other constitutional features associated with the reduced stress resistance of males of the Balb/c line compared to females [1; 5; 25].

A characteristic feature of the animals of both studied lines was a very significant excess of the weight coefficient of the spleen of females of a similar indicator in males. Unfortunately, we were unable to find a detailed explanation of this sexual difference in the literature, except for information about the more significant functional activity of the spleen of female Balb/c lines than in males [10; 26]. Another common feature of the animals of the studied lines was the presence of signs indicating more pronounced lymphoproliferative activity in the thymus of females compared to what was observed in males. These results are consistent with the ideas available in the literature about the different ratio of the activity of T- and B-cell processes in animals of different sexes – a shift in the ratio towards T-cell mechanisms in females and a shift in the ratio towards B-cell processes in males [5; 27; 28].

The results of comparing the studied indicators in same-sex animals of the C57Bl/6 and Balb/c lines indicated a greater severity of interline differences in females compared to males. In addition to constitutional differences in the total content of leukocytes, the males of the studied lines had features in the percentage of mononuclears (lymphocytes and monocytes) in the blood, as well as in the characteristics of the red blood germ. In our opinion, these features could reflect a higher adaptive status of animals of the C57Bl/6 line, which are known to be more stress-resistant compared to mice of the Balb/c line [1; 13; 14]. At the same time, the lower variability of indicators in male mice of the C57Bl/6 line could be due to the fact that all these animals developed AR increased activation, whereas in males of the Balb/c line the spectrum of antistress AR was wider.

The interlinear differences revealed in females also indicated a higher adaptive status of animals of the C57Bl/6 line. At the same time, the maximum values of the percentage of lymphocytes in the blood of females of both lines in combination with the dominance of mice of the C57Bl/6 line over animals of the Balb/c line in the weight characteristics of the thymus and the ratio of thymus and adrenal masses indicated that It was found that in females of the C57Bl/6 line, the development of AR increased activation occurred in the range of higher levels of reactivity of the organism than in Balb/c females. Moderate and low variability of indicators in mice of the C57Bl/6 line could reflect a high degree of

coincidence of the reactivity levels of these animals within the range, whereas high variability of indicators in females of the Balb/c line could, on the contrary, indicate noticeable differences in the reactivity levels at which AR increased activation developed in female mice of this line. It is likely that differences in the ranges of AR reactivity levels of females C57Bl/6 and Balb/c could to some extent affect the stress resistance of animals of the studied lines.

The lower variability of adaptive status indicators in mice of both sexes of the C57Bl/6 line compared to the variability of these indicators in animals of the Balb/c line could reflect the presence of more stable regulatory relationships in mice of the C57Bl line/6. According to the nonlinear dynamics of complex open (dissipative) systems, which include biological systems, such stable states are characterized by optimization of regulatory and metabolic processes, which ensures an energy-efficient mode of their functioning [29; 30].

The results of a comparative analysis of the biochemical parameters of the blood of female mice of the C57Bl/6 and Balb/c lines are of interest. They point to the peculiarities of the metabolism of the studied animals, which may be important for the reaction of mice of different lines to antitumor therapy. Thus, the interlinear differences in the activity of ALT and amylase could reflect the peculiarities of the ratio of carbohydrate and protein metabolism in animals belonging to different lines. It is known that carbohydrate metabolism differs the fastest. At the same time, the brain, characterized by a high intensity of energy metabolism and depleted of glucose and glycogen reserves compared to other tissues, consumes at least 50 % of free glucose from arterial blood [31]. In this regard, the shift towards carbohydrate metabolism in Balb/c mice obviously contributes to achieving a high level of brain energy metabolism and the realization of such a well-known feature of Balb/c mice as good learning ability [1].

Higher ALT activity than in animals of the Balb/c line in female mice of the C57Bl/6 line with a markedly reduced level of amylase activity indicated a shift in the metabolism of these animals towards protein metabolism. Thus, in mice of the C57Bl/6 line, a decrease in the provision of the brain with energy substrates was observed with an increase in the plastic resources of the body compared to what was observed in female mice of the Balb/c line. At the same time, a decrease in the overall body's need for "fast" energy obtained as a result of carbohydrate metabolism could be associated with the establishment of stable energy-efficient regulation regimes, which were mentioned above. This assumption is consistent with the known information about the relatively low energy metabolism and poor learning ability of mice of the C57Bl/6 line [32], characterized by more intense motor activity and more active behavior than mice of the Balb/c line [11; 33], as well as the relatively low variability of adaptation status indicators noted above. At the same time, the dominance of C57Bl/6 females over Balb/c mice in the activity of alkaline phosphatase and ALT, along with a higher level of lymphoproliferative processes in the thymus in these animals, could indicate an increase in the activity of all parts of the immune system (both T cells and B cells and neutrophils) [21; 22], and be important for the higher stress resistance of these animals compared to the stress resistance of Balb/c mice [1; 13; 14].

The revealed features of systemic regulation can have a noticeable effect on the mechanisms of nonspecific antitumor resistance and the effectiveness of antitumor treatment. Thus, the nature and intensity of the most stable ARs for a particular organism, the level of reactivity at which they develop, can significantly determine the functional state of the centers of autonomic regulation and peripheral links of the neuroendocrine and immune systems, modulating the state of tissues. In turn, the ratio of sympathetic and parasympathetic influences in tissue loci, the combination and activity of biochemical factors of the neuroendocrine and immune systems, metabolic products can contribute or, conversely, hinder the development of a malignant process [34; 35].

The peculiarities of metabolism may be important in connection with the important role of energy homeostasis of malignant cells and surrounding tissues in oncogenesis and the realization of the effects of therapy. In this regard, in recent years, attention has been increasing to the issue of metabolic concomitant therapy of oncological diseases [36; 37]. It has been shown that the metabolic background, the presence and type of energy substrates can be essential for the effectiveness of antitumor chemotherapy [38; 39]. At the same time, the means of metabolic therapy used in a number of severe chronic diseases can have an inhibitory effect on the

malignant process. In particular, a number of studies indicate the oncoprotective effect of metformin, which is a first-line drug for the treatment of type 2 diabetes [39; 40].

CONCLUSION

As a result of the study of intact mice of the C57Bl/6 and Balb/c lines of both sexes, along with sexual differences of a similar nature (the dominance of female mice over males in terms of weight characteristics of the thymus and spleen, the development of the most favorable antistress AR and the number of indicators with low variability), a number of interlinear features of the adaptive status and biochemical blood indicators. The interlinear features of the adaptive status indicated that in mice of the C57Bl/6 line, animals of different sexes had a similar character of AR (AR increased activation), which, however, developed at different levels of reactivity, whereas in mice of the Balb/c line, animals of different sexes differed in the nature of the prevailing antistress AR (in females – AR increased activation, in males, obviously – AR quiet activation and training). At the same time, in general, the revealed interlinear differences indicated a more favorable state of regulatory systems in mice of the C57Bl/6 line, which complements the known information about the higher stress resistance of these animals compared to mice of the Balb/c line. The interlinear features of the studied biochemical parameters of blood testified to the difference between female mice of the C57Bl/6 line and female mice of the Balb/c line in the ratio of carbohydrate and protein metabolism. The data obtained indicate a more active carbohydrate metabolism in Balb/c mice and a more intensive protein metabolism in C57Bl/6 mice.

The results of the analysis allow us to assume about some mechanisms that contribute to or hinder the stress resistance and learning ability of the studied animals. The revealed interlinear differences allow us to determine the directions for further study of the regulatory and metabolic characteristics of linear mice, which must be considered when choosing adequate experimental models for the development of effective methods of complex antitumor treatment.

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