THE EFFECT OF ALUMINUM- AND SILICON-CONTAINING ENTEROSORBENT ON THE THYMIC CELLULAR COMPOSITION IN MICE KEPT UNDER TWO-WEEK ALL-NIGHT LIGHTING

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ABSTRACT

Background. *Continuous lighting contributes to the development of desynchronosis, which is stressful for the body. As a result, the normal functioning of the immune system is disrupted, which in turn can shift the physiological balance towards pathology and endotoxemia. It is relevant to develop innovative drugs based on a sorbentmatrix, which can be modified with biologically active molecules that extendedly leave the sorbent surface. At the same time, the sorbent retains the properties of a detoxifier, fixing toxic agents on the surface and removing them from the body, which helps restore the internal environment and normalizes the overall reactivity of the body in extreme conditions.*

The aim. *To study the effect of aluminum- and silicon-containing enterosorbent (based on aluminum oxide and polydimethylsiloxane) on the cellular composition of the thymus and the distribution of thymocytes in the organ according to the cell cycling state in C57Bl/6 mice kept under the all-night lighting.*

Materials and methods. *Animals received sorbent (0.665 g per 1 kg of body weight in 200 µl of distilled water) through an intragastric tube once a day for 14 days against the background of continuous lighting. Intact mice and placebo animals composed control group. We used flow cytometry to assess the percentage of $CD3^{hi}$ and $CD3^{low}$ lymphocytes of the thymus, the $CD3^{low}/CD3^{hi}$ ratio, viability and distribution of cells across according to the cell cycling state.*

Results. *Continuous lighting inhibited the differentiation and maturation of young $CD3^{low}$ lymphocytes into mature forms of $CD3^{hi}$, reduced the proliferation of thymic epithelial cells, and activated apoptosis of lymphocytes and epithelial cells in the organ. The introduction of the sorbent restored the content and viability of young $CD3^{low}$ lymphocytes and contributed to the preservation of the viability and proliferation of thymic epithelial cells.*

Conclusion. *Using an enterosorbent based on aluminum oxide and polydimethylsiloxane under conditions of continuous lighting helps maintain the functional activity of the thymus, preventing its involution, and is advisable against the background of circadian disruption.*

Key words: *continuous two-week lighting, aluminum- and silicon-containing sorbent, $CD3^{hi}$ lymphocytes, $CD3^{low}$ lymphocytes, thymic epithelial cells, cell cycle, apoptosis, stress*

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ВЛИЯНИЕ АЛЮМИНИЙ-, КРЕМНИЙСОДЕРЖАЩЕГО ЭНТЕРОСОРБЕНТА НА КЛЕТОЧНЫЙ СОСТАВ ТИМУСА МЫШЕЙ, СОДЕРЖАВШИХСЯ ПРИ ДВУХНЕДЕЛЬНОМ КРУГЛОСУТОЧНОМ ОСВЕЩЕНИИ

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РЕЗЮМЕ

Обоснование. *Непрерывное освещение способствует развитию десинхроноза, что является стрессом для организма. Как следствие нарушается нормальная работа иммунной системы, что в свою очередь способно сдвигать физиологическое равновесие в сторону патологии и эндотоксикоза. Актуальна разработка инновационных лекарственных средств, в основе которых находится сорбентная матрица, которая может быть модифицирована биологически активными молекулами, пролонгированно покидающими поверхность сорбента. При этом сорбент сохраняет свойства детоксиканта, фиксируя на поверхности токсические агенты и выводя их из организма, что способствует восстановлению внутренней среды и нормализует общую реактивность организма в экстремальных условиях.*

Цель исследования. *Изучить влияние алюминий-, кремнийсодержащего энтеросорбента (на основе оксида алюминия и полидиметилсилоксана) на клеточный состав тимуса и распределение тимоцитов в органе по фазам клеточного цикла у мышей C57Bl/6, содержавшихся при круглосуточном освещении.*

Материалы и методы. *Животные получали сорбент (0,665 г на 1 кг веса тела в 200 мкл дистиллированной воды) через внутрижелудочный зонд 1 раз в день в течение 14 суток на фоне непрерывного освещения. Контролем служили интактные мыши и животные плацебо. Используя метод проточной цитометрии, оценивали процентное содержание $CD3^{hi}$- и $CD3^{low}$- лимфоцитов тимуса, соотношение $CD3^{low}/CD3^{hi}$, жизнеспособность и распределение клеток по фазам клеточного цикла.*

Результаты. *Круглосуточное освещение угнетало процессы дифференцировки и созревания молодых лимфоцитов $CD3^{low}$ в зрелые формы $CD3^{hi}$, снижало пролиферацию эпителиальных клеток тимуса, активировало апоптоз лимфоцитов и эпителиальных клеток в органе. Введение сорбента восстанавливало содержание и жизнеспособность молодых $CD3^{low}$-лимфоцитов и способствовало сохранению жизнеспособности и пролиферации эпителиальных клеток тимуса.*

Заключение. *Применение энтеросорбента на основе оксида алюминия и полидиметилсилоксана в условиях непрерывного освещения способствует сохранению функциональной активности тимуса, препятствуя его инволюции, и целесообразно на фоне нарушения суточных ритмов режима освещения.*

Ключевые слова: *непрерывное двухнедельное освещение, алюминий-, кремнийсодержащий сорбент, $CD3^{hi}$-лимфоциты, $CD3^{low}$-лимфоциты, эпителиальные клетки тимуса, клеточный цикл, апоптоз, стресс*

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INTRODUCTION

Circadian desynchrony is becoming increasingly common due to the changing conditions of modern 24-hour society, including exposure to artificial lighting, shift work, and time zone changes. Suppression of melatonin synthesis due to prolonged exposure to continuous light leads to the light-induced functional desynchronosis development, which is stress for the body [1]. An unbalanced response to severe or prolonged stress can shift the physiological balance towards pathology and endotoxicosis development. It has been shown that a decrease or blockade of melatonin synthesis accompanies the development of numerous common pathologies – from aging and type 2 diabetes mellitus to neurological disorders [2, 3]. Neurohumoral mechanisms play a major role in maintaining the functional and biochemical stability of the body in changing environmental conditions, and the pituitary-adrenal axis activity is considered to be the basis of the adaptive response to stress. Long-term and/or strong exposure activates the secretion of cortisol and corticosterone by the adrenal glands, which exert their metabolic influence on cells and organs, including causing a decrease in the thymus functional activity [4]. The basis for the thymus gland involution is considered to be excessive apoptosis and proliferation inhibition of a subpopulation of cortisol-sensitive lymphocytes [5].

The thymus is a central organ of lympho-/immunopoiesis, in which proliferation and selection of antigen-specific and host antigen-tolerant lymphocytes ensures migration of mature and naive T-cells into the bloodstream and peripheral lymphoid organs, where T-cells provide both cellular and humoral immune responses by activating B-lymphocytes. Thymus involution can contribute to the risk and recurrence of cancer, increased susceptibility to infections [6], and immunocompetence loss can lead to the development of a wide range of immune and severe infectious diseases, obesity and diabetes [5, 7]. Aging and fatty degeneration of the thymus become a factor in maintaining inflammation and the development of "aging" diseases – arthritis, and cardiovascular diseases [8].

In connection with the above, there is a clinical need for non-toxic and affordable means capable of reducing the stress impact on the body. Scientific research by academician Yu.I. Borodin and his students have shown that sorbent treatment methods are directly related to the possibility of overcoming endotoxicosis syndrome. Enterally administered sorbent is capable of influencing the physiological constants of the body, not even directly related to the enterosorption process. In this case, the sorbent acts as a trigger for a cascade of reactions from the local to the organism level. There is a functional analogy in the action of the sorbing agent and the regional lymphatic apparatus. In both cases, drainage and detoxification of the pathological focus take place [9, 10].

Currently, the interest of researchers is aimed at developing innovative drugs based on a sorbent matrix modified with biologically active molecules that leave the sorbent surface for a prolonged period. The sorbent itself (as an enterosorbent) retains the properties of a detoxifier, fixing a wide class of substances on its surface – from low-molecular to high-molecular, found in excess in various diseases and poisonings (for example, bacterial toxins, bilirubin, catecholamines, kinin, bile acids), and removing them from the body. From this point of view, a promising hydrophilic-hydrophobic aluminum-, silicon-containing sorbent (enterosorbent) based on aluminum oxide and polydimethylsiloxane – Al_2O_3@PDMS with a pore volume of 0.2 cm^3/g, capable of binding molecules of different charges and different sizes – from low- to high-molecular. The adsorption activity, for example, in relation to low-molecular methylene blue, is 10 mg/g; and it absorbs *Staphylococcus aureus* from the aqueous medium by 25 % of their initial content. This sorbent, used as a carrier for lithium, has successfully passed preclinical studies as part of a drug within the framework of a state assignment. The enterosorbent itself is safe, belongs to hazard class IV. This free-flowing white powder with a particle size of 0.04 mm and a specific surface area of 100 m^2/g can be used as a component of drugs. Of interest is the study of its biological properties in relation to vulnerable thymus cells under conditions of disruption of natural day-night biorhythms.

The aim of this work was to study the effect of aluminum-, silicon-containing enterosorbent Al_2O_3@PDMS on the thymus cellular composition and the distribution of thymocytes in the organ according to the cell cycle phases in C57Bl/6 mice kept under continuous lighting.

THE METHODS OF THE STUDY

The study was conducted at the SPF Vivarium of the Federal Research Center Institute of Cytology and Genetics, Siberian Branch of Russian Academy of Sciences (RFMEFI61914X0005 and RFMEFI62114X0010) and complied with the requirements of Directive 2010/63/EU of the European Parliament and of the Council of the European Union on the protection of animals used for scientific purposes and good laboratory practice. The experimental protocol was approved by the Ethics Committee of the Research Institute of Clinical and Experimental Lymphology, a branch of the Institute of Cytology and Genetics, Siberian Branch of Russian Academy of Sciences (Protocol No. 128 dated March 15, 2017). Male C57Bl/6 mice aged 10–12 weeks were kept in controlled barrier rooms with free access to water and food.

Some mice were kept under continuous lighting conditions (CL; $n = 6$) created by Philips 18 W fluorescent lamps (Philips, Netherlands; light : dark photoperiod 24 : 0 h) for 14 days. The second group of animals (CL + Sorbent; $n = 6$) were given a sorbent composition of aluminum oxide and polymethylsiloxane (0.665 g per 1 kg of body weight in 200 µl of distilled water intragastrically daily against the background of CL for 14 days. Animals that received 200 µl of distilled water intragastrically

daily against the background of continuous lighting were selected as a placebo group.

The third group consisted of intact mice (Control; $n = 6$) kept under standard lighting and feeding conditions (light : dark photoperiod 14:10 h). The animals were removed from the experiment by craniocervical dislocation, the thymus was removed, and a cell suspension was prepared, which was examined using a CytoFlex S100 flow cytometer (Beckman Coulter, USA).

The thymus was homogenized in cold phosphate-buffered saline (PBS) in a glass homogenizer at 4°C. Thymocytes were pelleted by centrifugation (300 g, 5 min) and used for staining with CD3e-APC monoclonal antibodies (BioLegend, USA) to identify young $CD3^{low}$- and mature $CD3^{hi}$-lymphocytes. To analyze cell distribution across cell cycle phases, thymus cells (5 × 106) were fixed in cold 70 % ethanol for 24 h [11].

Cell samples (2 06) in 100 µl were stained with fluorescently labeled antibodies for 30 min at room temperature in the dark. They were then washed twice with PBS and analyzed on a flow cytometer. Cells fixed with 70 % ethanol were centrifuged (300 g, 7 min), washed with PBS and incubated in hypotonic extraction buffer for 5 min to remove low molecular weight DNA to determine the subdiploid peak. The cells washed with buffer were incubated (30 min, room temperature, dark) in staining buffer containing 50 µg/mL propidium iodide (PI; Sigma-Aldrich, USA) and 200 µg/mL RNase-A (Invitrogen, USA). PI fluorescence was determined using a flow cytofluorimeter (λEm = 670 nm). The number of cells with different DNA content in the cell cycle phases: SubG1, G0/G1, S, G2/M was estimated.

Statistical processing of the obtained results was performed in the Statistica 12.0 program (StatSoft Inc., USA). The values of the median, first and third quartiles were determined. The statistical significance of the differences in the compared values between the groups CL + Sorbent and CL, CL + Sorbent and Control was calculated using the nonparametric Mann – Whitney U-test. Differences were considered statistically significant at $p < 0.05$.

RESULTS

1. The effect of taking a sorbent composition on the numerical density of $CD3^{low}$- and $CD3^{hi}$-lymphocytes in animals with continuous lighting

In the previous work [12], it was found that continuous lighting of mice for 14 days led to a statistically significant decrease in the relative number of both young $CD3l^{low}$ ($p = 0.0051$) and mature $CD3^{hi}$ ($p = 0.0374$) T lymphocytes in the thymus compared to the control. At the same time, the $CD3^{low}/CD3^{hi}$ ratio decreased statistically significantly ($p = 0.0131$). The development of accidental thymus involution in mice with CL was not registered in our study. Intragastric administration of enterosorbent to animals against the background of CL normalized the relative number of young $CD3^{low}$ thymocytes, increasing their content to 46.70 (45.88; 47.08) % (in intact animals – 43.40 (41.85; 44.33) %). As a result, the $CD3^{low}/CD3^{hi}$ ratio increased significantly (compared to control $p = 0.0202$; compared to CL $p = 0.0051$) (fig. 1).

Such changes can include disruption of daily biorhythms, proliferation and destruction of immune system cells under altered light conditions, as well as prolonged stress leading to proliferation inhibition of immature lymphocytes in the thymus cortex and their increased apoptosis.

To determine the sorbent effect on the survival and proliferation of thymus cells under 14-day continuous lighting, we performed a cell cycle analysis for all thymus cells.

2. The effect of the sorbent composition administration on the cell cycle of thymus cells under continuous lighting conditions

Cell cycle analysis of the entire population of thymus cells in mice after CL showed a significant decrease in the relative number of cells in the phase S to 3.4 (2.3; 6.8) % compared to the control – 7.3 (7.0; 11.1) % ($p = 0.0367$), a more than threefold increase in the proportion of cells in the apoptosis stage to 2.2 (1.8; 3.2) % compared to the control – 0.7 (0.63; 0.73) % ($p = 0.01997$).

Sorbent administration to animals against the background of CL normalized the cell cycle, increasing the percentage of cells in the phase S to 7.45 (6.5; 12.75) % and reducing the number of cells in the apoptosis stage to the control level. Thus, the sorbent maintains an increased adaptive level of thymus cell proliferation and protects cells from apoptosis under prolonged continuous lighting conditions.

For a more complete analysis of the proliferation and viability of thymus cell elements on the flow cytometry histograms, all cells were divided into 3 groups (3 gates – PLym, P2Lym, P3big) depending on their size and corrected for the cell cycle (fig. 2). Thus, the PLym gate was formed by the smallest cells, some of which were in the active cell cycle phases (S + G2/M). Young $CD3^{low}$ lymphocytes were contained mainly in this gate. The P2Lym gate contained mature non-dividing lymphocytes in the G0/G1 stage. The largest cells, most of which were actively dividing, formed the P3big gate. Figure 2 shows the cell cycle of each gate.

The gate of the smallest PLym cells, containing $CD3^{low}$ lymphocytes, had the lowest cell count compared to other groups; the number of cells in the phase S was 6.8 (6.28; 7.1) %, and cells in the apoptotic stage were 2.2 (1.5; 2.75) % in control animals. Continuous lighting inhibited the phase S, resulting in a decrease in the relative number of cellular elements to 6.05 (5.55; 6.10) %, and a statistically significant increase in the number of cells in the PLym gate in the apoptotic state to 11.65 (9.05; 13.28) % ($p = 0.0051$). Sorbent administration against the background of CL contributed to the proliferation restoration of thymus lymphocytes

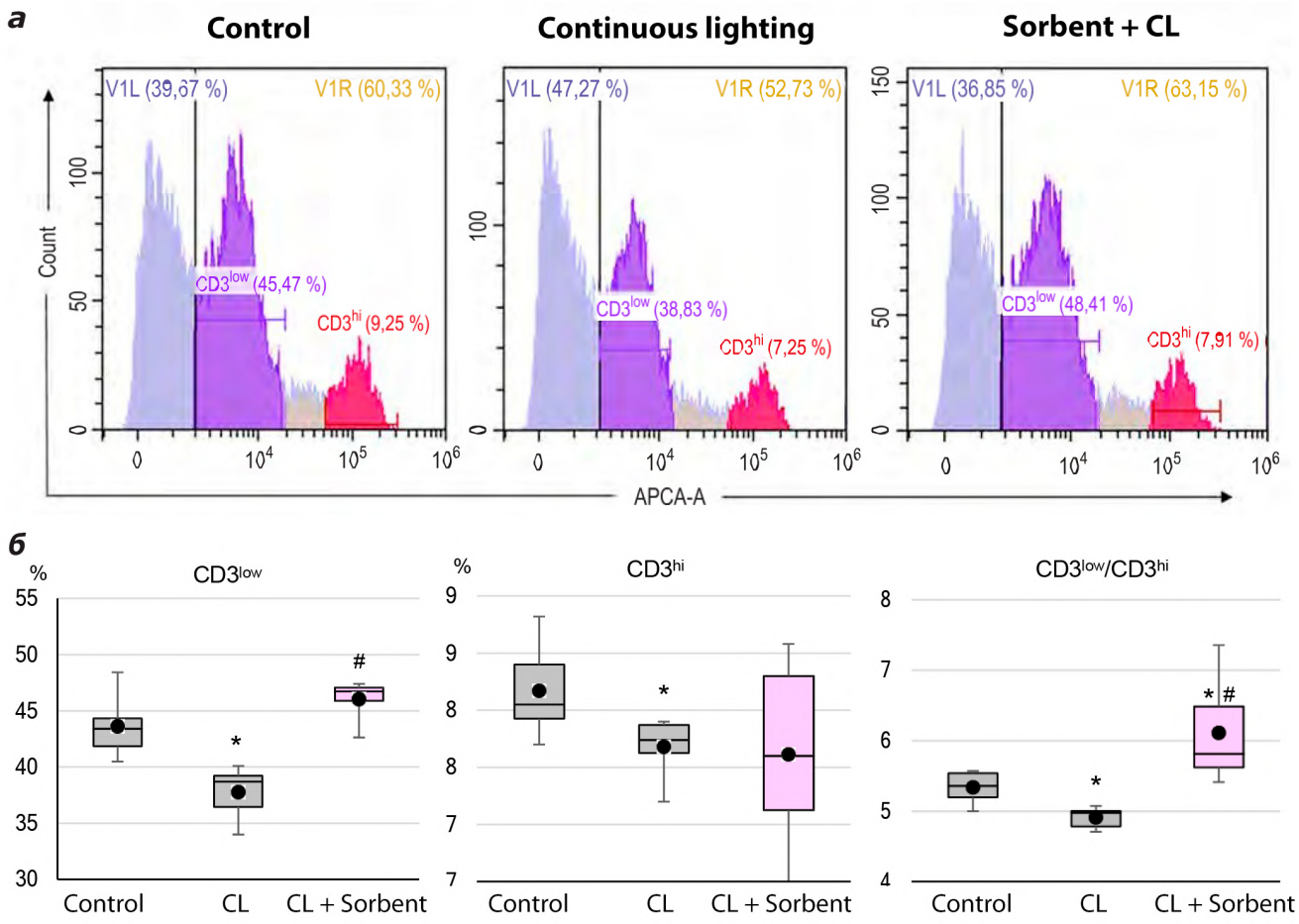

FIG. 1.
Thymus of C57Bl/6 mice treated with sorbent against the background of continuous lighting (CL): ***а*** *– histograms of distribution of $CD3^{low}$ and $CD3^{hi}$ lymphocytes;* ***б*** *– relative number of $CD3^{low}$ and $CD3^{hi}$ lymphocytes and $CD3^{low}/CD3^{hi}$ ratio; * – compared to the control; # – compared to CL ($p < 0.05$)*

and an increase in their viability, as a result the relative content of cellular elements in the phase S increased to 8.85 (7.75; 11.75) % and the percentage of cells in the apoptosis stage decreased to 4.5 (3.4; 4.85) % ($p = 0.0065$).

From Figure 2 it can be seen that long-term continuous lighting inhibited the relative number of T lymphocytes (PLym gate) in the phase S, but did not affect the content in the G2/M phase, i.e., in essence, there was an inhibition of proliferation (residual proliferation). The sorbent against the background of CL caused a significant increase in the number of cells in both phases S and G2/M (phase G2/M in the control – 0.85 (0.73; 1.05) %, in the CL group – 1.05 (0.63; 1.25) %, in the CL + Sorbent group – 1.7 (1.23; 2.63) %. Such changes are possibly associated with an adaptive response to stress. A wide range of data in the sorbent presence indirectly indicates that its action in this case is not direct and is not aimed at a specific target, but helps the body to remain at the adaptation stage and not slide to the exhaustion stage, sorbing and removing excess amounts of highly active substances.

3. The sorbent composition effect on the viability and proliferation of thymus epithelial cells under continuous lighting

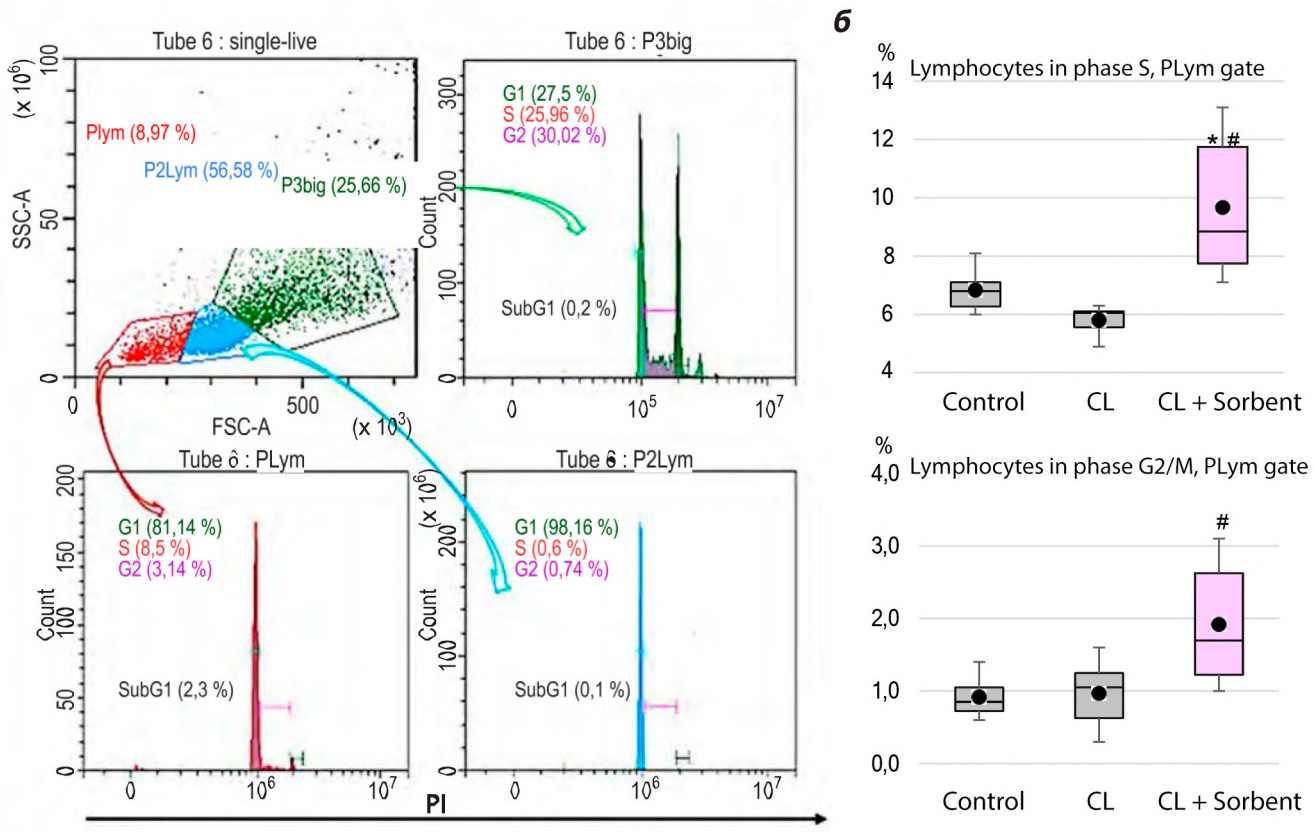

FIG. 2.
а *– flow cytometry histograms of the thymus cell cycle of C57Bl/6 mice: gating the thymus cells by size on the histogram in SSC/FSC coordinates; cell cycle histograms are presented for each selected region of thymus cells (shown by arrows): ordinate axis – the number of cells; abscissa axis – the fluorescence intensity of propidium iodide.* ***б*** *– histograms of the percentage of Plym gate lymphocytes in the S and G2/M cell cycle stages; * – compared to the control, # – compared to continuous lighting (CL) group (p < 0.05)*

Proliferation, differentiation and development of lymphocytes immunotolerant to the host with a wide range of TSR antigens occur in close contact with the epithelial cells of the thymus. In this case, negative selection of T-lymphocytes occurs in the medullary niches due to the expression of MHC-I (major histocompatibility complex) and MHC-II molecules on the surface, and cortical epithelial cells are responsible for positive selection. Maintenance of the cortical and medullary epithelial niches of the thymus is provided by epithelial cell precursors with long-term renewal and a high proliferation and differentiation rate with an estimated replacement time of one to two weeks from the first weeks of life. Maintenance of the epithelium of the thymus medulla in adults is provided by epithelial precursors that have lower self-renewal rates, but still retain a high proliferation rate [13].

In our study, the proliferative potential of the P3big gate cells was significantly higher than that of the PLym or P2Lym gate cells. The cellular elements of the P3big group are larger and can be macrophages, dendritic cells, and epithelial cells that make up the thymus stroma and provide an appropriate microenvironment for developing lymphocytes. The high proliferation rate indicates that these cellular elements are most likely epithelial cells, which are the main cells of the thymus niches. Continuous lighting had a negative effect on the organ stroma, statistically significantly reducing the numerical density of epithelial cells in the phase S to 26.55 (19.40; 27.55) % compared to the control – 32.50

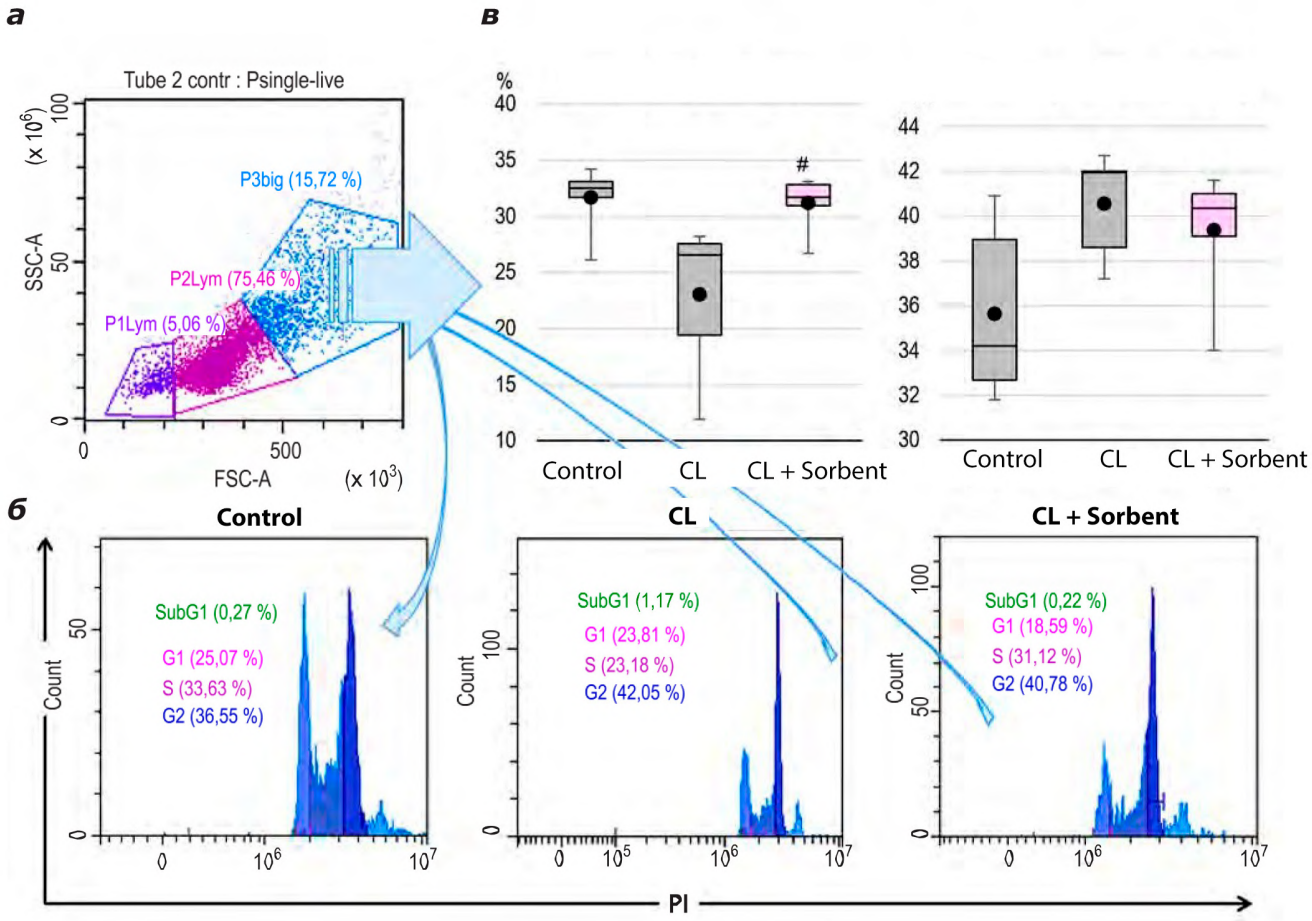

FIG. 3.
Flow cytometry histograms: ***а*** *– histogram of distribution of thymus cells in FSC/FSC coordinates, P3big gate is highlighted;* ***б*** *– histograms of distribution of P3big gate cells by phases of the cell cycle: ordinate axis – the number of cells, abscissa axis – propidium iodide;* ***в*** *– graphs of the relative number of P3big gate cells in the S and G2/M cell cycle stages: * – compared to the control, # – compared to continuous lighting (CL) group (p < 0,05)*

(31.68; 33.10) % (p = 0.0202). Sorbent administration against the background of CL normalized the proliferation of thymus epithelial cells, restoring their percentage in the phase S to 31.70 (30.95; 32.83) % (fig. 3). The content of epithelial cells in the G2/M phase did not change statistically significantly compared to the other groups of animals. Long-term and continuous lighting led to an increase in the content of epithelial cells at the apoptosis stage to 0.9 (0.73; 1.18) % (p = 0.0051). Sorbent administration against the background of continuous lighting contributed to a decrease in apoptosis to the control level (0.23 (0.22; 0.29) %; p = 0.0051).

Therefore, sorbent use against the background of long-term exposure to continuous lighting is advisable, since the sorbent supports the self-renewal of thymus epithelial cells, maintaining a high rate of epithelial cell proliferation and reducing apoptosis to the values of intact animals (fig. 3).

DISCUSSION

The results of the present study showed a connection between long-term disruption of circadian rhythms, disruption of thymus functioning and the sorbent normalizing role to support proliferation and preserve the viability of early precursors of T lymphocytes and epithelial cells of the thymus niches. A decrease in the body's resistance to any stress, in particular, with CL, is associated with insufficient functional activity of the thymus.

Previously, we showed that blockade of melatonin synthesis in mice under continuous lighting inhibits the processes of differentiation and maturation of young $CD3^{low}$ lymphocytes into mature $CD3^{hi}$ forms, leads to increased apoptosis of T lymphocytes in the thymus and, as a consequence, to leukopenia [12]. Under these conditions, the hypothalamic-pituitary-adrenal (HPA) axis is activated as part of the stress response, in which pituitary hormones stimulate the adrenal cortex to release glucocorticoids, including cortisol. Excess cortisol causes apoptosis of cortisol-sensitive early lymphocytes, which leads to T-cell immunity deficiency. This cortisol effect is considered to be a driver of thymus involution [4, 5, 14]. However, long-term continuous lighting affected not only a decrease in proliferative activity and apoptosis of young $CD3^{low}$ lymphocytes, but also a decrease in the proliferation of epithelial cells, which are the basis of both the cortical and medullary niches, which are important for maintaining the proliferation and selection of T lymphocytes. The sorption therapy use against the background of continuous lighting had a positive effect on these parameters. A possible protective mechanism of the sorbent use may be both the sorption and removal of excess cortisol, and a deeper effect mediated by the state and activity of the intestinal microbiota. Previous studies have shown that the use of the carbon-mineral sorbent SUMS-1 (based on aluminum oxide) increases the number of intestinal epithelial villi, normalizing the microbiome state [15]. Microbes have been shown to have a close relationship with the HPA axis [16]. Intervention in the intestinal microbiota can significantly affect the treatment of stress-related diseases. Stress causes changes in HPA axis hormones towards an increase in cortisol in germfree mice [17]. In addition, intestinal microbes regulate tryptophan metabolism, produce dopamine, γ-aminobutyric acid, histamine and acetylcholine, which affect the central nervous system function and the HPA axis stability [18]. On the other hand, stress itself can negatively affect the intestinal microbiome, inhibiting the vital activity of microbes, changing their secreted profile [19]. Based on the results of this study, it can be assumed that the sorbent created on the basis of aluminum oxide and polymethylsiloxane, sorbing oxidants, toxic metabolites, providing a detoxifying and lymphatic drainage effect, promotes proliferation and maintains the viability of early precursors of lymphocytes and epithelial cells of the thymus.

CONCLUSION

The conducted studies of the efficiency of porous hydrophilic-hydrophobic sorbent using based on combustion oxide and polydimethylsiloxane Al_2O_3@PDMS under conditions of long-term exposure to stress caused by continuous lighting for 14 days. The sorbent use ensures the thymus function preservation, maintaining the integrity and proliferation of young lymphocytes and epithelial cells of this section. The obtained data allow for preventive sorption therapy against the background of circadian rhythm disorders when changing time zones in people working at night or in urban northern regions with expected fluctuations in lighting throughout the year, helping to maintain the body's own stress forces, normalizing cellular immunity.

Conflicts of interest

No potential conflict of interest relevant to this article reported.

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