EFFECT OF DIFFERENT LIGHTING REGIMEN AND MELATONIN INTRODUCTION ON THE DENSITY OF MELATONIN RECEPTORS IN NEURONS OF THE PREVENTRICULAR NUCLEUS OF THE RATS' HYPOTHALAMUS

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The aim of the study *– to describe in number the density of melatonin receptors in the subnuclei of the preventricular nucleus of the rats'hypothalamus under various illumination regimen and melatonin introduction.*

Material and methods*. The experiments were conducted on male white rats aged 24-27 months. The animals of the first group (intact) stayed for 14 days under normal light conditions (light-darkness in 12 hours, LD, illumination from 08.00 to 20.00 by means of fluorescent lamps, the level of illumination in the cells with animals was 500 lux). The animals of the second group were kept in constant darkness for the same period (light deprivation, DD, induction of the pineal gland hyperfunction). The rats of the third group were kept in conditions of constant light of similar intensity for seven days (LL, induction of the pineal gland hypofunction). The animals of the fourth group stayed under the same experimental conditions as the rats of the third group. They were given melatonin (Sigma, USA, purity level – 99.5%) intraperitoneally at a dose of 1.5 mg/kg in 1.0 ml of solvent (0.9% ethanol solution in physiological saline). After the end of the 14-day period, the animals were taken out from the experiment at 14.00 and 02.00 the next day by performing decapitation under ethaminal anesthesia (40.0 mg/kg, intraperitoneally). All stages of the experiment were carried out according to the basic requirements of the European Convention on the Humane Treatment of Animals. Protocol of the research work approved by the Commission on Biomedical Ethics questions, BSMU. Dated 24.02.2019, №2. Melatonin 1A receptors in the medial small cell subnuclei of the paraventricular nucleus of the hypothalamus dentified by immunohistochemistry using polyclonal antibodies (Abcam, Great Britain) and the LSAB2 streptavidin-biotin imaging system (peroxidase label + diaminobenzidine) (Chemicon International Inc., USA). Mayer's hematoxylin was used for additional staining of nuclei. Quantitative studies of staining intensity were performed by computer microdensitometry. The intensity of specific staining (the "Optical Density" index) was identified with the degree of melatonin receptors density. Taking into consideration the requirement of performing multiple statistical comparisons of the mean values in statistical samples, the Newman-Keuls criterion was used to determine differences between populations.*

Results. *The density of melatonin 1A receptors in the hypothalamus neurons of rats under study according to the illumination regimen has been distinguished with clear twenty-four-hour fluctuation. Illumination regimen change resulted into its marked abnormalities. On conditions of the persistent illumination, the density of the structures under study is probably lower than under light deprivation.*

When using melatonin, immunohistochemical analysis at 02.00 denoted a probable increase in the optical density of the specific staining in the medial small-cellular subnuclei of the preventricular nucleus of rats' hypothalamus as to such in animals not injected with melatonin against a background of light stress (0.252±0.0023 and 0.188±0.0025 rel.un. optical density, respectively). Simultaneously, when correcting changes, caused by light stress in the lateral large-cellular subnuclei of the preventricular nucleus of rats' hypothalamus, with melatonin, a tendency to normalization of index, which at night constituted 0.253±0.0026 rel.un. optical density, and in the daytime it significantly decreased and was within the range of 0.226±0.0021 rel.un. optical density, was observed.

Conclusion*. The density of melatonin 1A receptors in the medial small-cellular subnuclei of the paraventricular nucleus of the rats' hypothalamus in health is regulated with a distinct circadian structure. The highest indices of melatonin receptors' density were registered at 02.00 o'clock of twenty-four-hour, while at 14.00 o'clock the density probably reduced.*

Expressed desynchronization of fluctuations of melatonin receptors density in twenty-

Key words: *preventricular nucleus, photoperiod, melatonin, receptors.*

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four- hour was observed in photoperiod modification. The optical density of specific staining is probably stably lower during prolonged light exposure in comparison with both control index and as that during light deprivation.
When using melatonin on condition of prolonged light exposure, a veritable increase of the index was marked compared to that in animals which were not given melatonin against a background of light stress, simultaneously a tendency towards normalization of the index was observed.

***Ключові слова**: пришлуночкове ядро, фотоперіод, мелатонін, рецептори.*

ВПЛИВ РІЗНОГО РЕЖИМУ ОСВІТЛЕННЯ ТА УВЕДЕННЯ МЕЛАТОНІНУ НА ЩІЛЬНІСТЬ МЕЛАТОНІНОВИХ РЕЦЕПТОРІВ У НЕЙРОНАХ ПРИШЛУНКОВОГО ЯДРА ГІПОТАЛАМУСА ЩУРІВ

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Клінічна та експериментальна патологія 2025. Т.24, № 3 (93). С. 64-70.

Мета роботи *– кількісно охарактеризувати щільність мелатонінових рецепторів у суб'ядрах пришлуночкового ядра гіпоталамуса щурів за різного режиму освітлення та уведення мелатоніну.*
Матеріал та методи*. Експерименти проводили на самцях білих щурів віком 24-27 місяців. Тварини першої групи (інтактні) перебували протягом 14 днів за нормальних умов освітлення (світло-темрява протягом 12 годин, світлова депривація, освітлення з 08.00 до 20.00 за допомогою люмінесцентних ламп, рівень освітлення в камерах із тваринами становив 500 люкс). Тварини другої групи перебували в постійній темряві протягом такого ж періоду (світлова депривація, індукція гіперфункції шишкоподібної залози). Щурів третьої групи утримували в умовах постійного світла протягом семи днів (індукція гіпофункції епіфіза). Тварини четвертої групи перебували в тих же експериментальних умовах, що й щурі третьої групи. Їм вводили мелатонін (Sigma, США, рівень чистоти – 99,5%) внутрішньочеревно у дозі 1,5 мг/кг в 1,0 мл розчинника (0,9% розчин етанолу у фізіологічному розчині). Після закінчення 14-денного періоду тварин виводили з експерименту о 14:00 та о 02:00 наступного дня). Усі етапи експерименту проводили відповідно до основних вимог Європейської конвенції про гуманне поводження з тваринами. Протокол наукового дослідження затверджений Комісією з питань біомедичної етики БДМУ 24.02.2019 року, №2. Рецептори мелатоніну 1А у медіальних дрібноклітинних суб'ядрах пришлуночкового ядра гіпоталамуса щурів ідентифікували імуногістохімічним методом із використанням поліклональних антитіл (Abcam, Велика Британія) та системи візуалізації стрептавідин-біотину LSAB2 (пероксидазна мітка + діамінобензидин) (Chemicon International Inc., США). Для додаткового фарбування ядер використовували гематоксилін Майєра. Кількісні дослідження інтенсивності фарбування проводили за допомогою комп'ютерної мікроденситометрії. Інтенсивність специфічного фарбування (індекс "Оптичної щільності") ідентифікували зі ступенем щільності рецепторів мелатоніну. Враховуючи необхідність проведення багаторазових статистичних порівнянь середніх значень у статистичних вибірках, для визначення відмінностей між популяціями використовували критерій Ньюмена-Кеулса.*
Результати. *Щільність рецепторів мелатоніну 1А у досліджуваних нейронах гіпоталамуса щурів за стандартного режиму освітлення відзначалася чіткими добовими коливаннями. Зміна режиму освітлення призвела до вираженого їх порушення. За умов постійного освітлення щільність досліджуваних структур вірогідно менша, ніж при світловій депривації. При застосуванні мелатоніну імуногістохімічний аналіз о 02.00 год показав вірогідне зростання оптичної щільності специфічного забарвлення у медіальних дрібноклітинних суб'ядрах пришлуночкового ядра гіпоталамуса щурів щодо до такої у тварин, яким не проводили ін'єкції мелатоніну на фоні світлового стресу (0,252±0,0023 і 0,188±0,0025 в.о.опт.щільності відповідно). Водночас, при корекції мелатоніном змін, спричинених світловим стресом у латеральних великоклітинних суб'ядрах пришлуночкового ядра гіпоталамуса щурів, спостерігали тенденцію до нормалізації показника, який вночі становив 0,253±0,0026 в.о.опт. щільності, а вдень вірогідно знижувався і перебував у межах – 0,226±0,0021 в.о.опт. щільності.*
Висновки. *1. Щільність рецепторів мелатоніну 1А у медіальних дрібноклітинних*

суб'ядрах пришлуночкового ядра гіпоталамуса щурів у нормі підпорядкована чіткій циркадіанній організації. Найвищі показники щільності рецепторів мелатоніну відмічали о 02.00 год доби, водночас о 14.00 год вона вірогідно знижується. 2. За модифікації фотоперіоду спостерігали виражений десинхроноз коливань щільності рецепторів мелатоніну впродовж доби. Порівняно як з контрольним показником, так і з таким при світловій депривації, при тривалій експозиції світлом оптична щільність специфічного забарвлення вірогідно стабільно нижча. 3. При застосуванні мелатоніну за умови тривалого експозиції світлом відзначали вірогідне збільшення показника порівняно з таким у тварин, яким на фоні світлового стресу не уводили мелатонін, водночас спостерігали тенденцію до нормалізації показника.

Introduction

Preventricular (paraventricular) nuclei of the hypothalamus are the highest center of coordination of vegetative functions that are directly involved in neuroendocrine regulation, in particular, under stress conditions [1-3]. These structures have a complex cellular organization and include lateral large-cell and medial small-cell subnuclei, the neurons of which differ not only in size and efferent innervation, but also in the spectrum of synthesized neuropeptides [4, 5]. These special features determine the important role of neuronic populations - subnuclei not only in the endocrine regulation of the tropic function of the adenohypophysis, but also in the implementation of the body's neuroendocrine response to stress of various genesis [6]. Among the hormonal links of the stress response, a stress-implementing component associated with the participation of corticotropin-releasing hormone, which activates the pituitary-adrenocortical system, and hormones of the stress-limiting system, including melatonin [7-9], are distinguished. This is a multifunctional hormone, since its receptors are present in neurons of various brain structures. The highest hormone level and the density of melatonin receptors have been identified in the anterior hypothalamus [10].

The pineal gland (pineal gland of the brain) receives multisynaptic tracts through the ventricular nuclei that participate in the regulation of the night synthesis of the pineal hormone - melatonin and the inhibition of this process in conditions of increased lighting [11]. Melatonin controls the state of the hypothalamic-pituitary system, as well as the activity of the endocrine glands through melatonin receptors (membrane, cytosolic and nuclear). According to the feedback mechanism, melatonin is involved in the regulation of the activity, properly the preventricular nuclei of the hypothalamus. Autoradiographic and radioimmune studies have made it possible to identify the presence of melatonin receptors (MT1, MT2, MT3) in various structures, especially in such as the human brain, intestines, ovaries, blood vessels, etc. Scientists suggest that the melatonin receptors of the preventricular nucleus are involved in the regulation of circadian rhythms [12, 13]. However, there is practically no information concerning characteristics of melatonin receptors in the subnuclei of the paraventricular nucleus of the hypothalamus of old rats.

Question of a comprehensive research of the neurons' subpopulations of the hypothalamic preventricular nucleus that synthesize stress-releasing hormones, what is, in its turn, initiators of the body's stress reactions, is a question of urgent importance when studying stress reactions and effects of stress-limiting factors (in particular, melatonin). Corticoliberin belongs to a number of leading peptides that show their effect in the regulation of corticotropin production [6, 14]. The mark, immunoreactive to corticoliberin, is identified, mainly, in the medial small-cell subnucleus of the hypothalamic preventricular nucleus. Morphofunctional changes that do not have clear explanation in the available literature, occur in the neurosecretory cells of the preventricular nucleus under the light influence. in different photoperiod length in old rats.

The aim of the work

To describe quantitatively the density of melatonin receptors in the subnuclei of the preventricular nucleus of the rats' hypothalamus at different lighting conditions and melatonin administration.

Research materials and methods

The experiments were conducted on male white rats aged 24-27 months. The animals were kept in standard vivarium conditions at constant temperature and humidity and free access to water and food. The experimental rats were divided into four groups, each of which, in its turn, consisted of two subgroups (six animals).

The animals of the first group (intact) stayed for 14 days under normal light conditions (light-darkness in 12 hours, LD, illumination from 08.00 to 20.00 by means of fluorescent lamps, the level of illumination in the cells with animals was 500 lux). The animals of the second group were kept in constant darkness for the same period (light deprivation, DD, induction of the pineal gland hyperfunction). The rats of the third group were kept in conditions of constant light of similar intensity for seven days (LL, induction of the pineal gland hypofunction). The animals of the fourth group stayed under the same experimental conditions as the rats of the third group. They were given melatonin (Sigma, USA, purity level – 99.5%) intraperitoneally at a dose of 1.5 mg/kg in 1.0 ml of solvent (0.9% ethanol solution in physiological saline).

For the purpose of detecting circadian differences in melatonin receptors and taking into account the cyclical nature of melatonin production, after the end of the 14-day period, the animals were taken out from the experiment at 14.00 and 02.00 the next day by performing a single-stage decapitation under ethaminal

anesthesia (40.0 mg/kg, intraperitoneally). All stages of the experiment were carried out according to the basic requirements of the European Convention on the Humane Treatment of Animals. Protocol of the research work approved by the Commission on Biomedical Ethics questions, BSMU. Dated 24.02.2019, №2.

Fragments of the cerebral hemispheres with a section of the hypothalamus were fixed in a 10% solution of neutral buffered formalin during 22 hours for immunohistochemical studies. After that, accelerated dehydration was performed in alcohols of increasing concentration, embedded in paraffin at a temperature of 58°-C, followed by obtaining histological sections 5 μm thick.

For the purpose of performing immunohistochemical technique, polyclonal antibodies to melatonin receptors 1A of Abcam (Great Britain) producer and streptavidin-biotin visualization system LSAB2 (peroxidase label + diaminobenzidine) of Chemicon International Inc. (USA) producer were used. The standardization of the technique protocol for all sections was maximally adhered to. Mayer's hematoxylin was used for additional staining of nuclei.

Quantitative studies of the staining intensity were carried out according to the following trial design. First, using a microscope objective x40, digital copies of the optical image were obtained, subsequently analyzed by means of a licensed copy of the computer program, namely – computer microdensitometry was performed. The analysis was carried out on the basis of the microprobe technique measurements in places of positive staining according to the "Optical Density" index (in relative units with a range of 0-1, moreover, "0" corresponds to the absolute optical transparency in the microprobe, and "1" - absolute optical opacity). The intensity of specific staining (the "Optical Density" index) was identified with the degree of melatonin receptors density.

Taking into consideration the requirement of performing multiple statistical comparisons of the mean values in statistical samples, the Newman-Keuls criterion was used to determine differences between populations.

Investigation was conducted within the limits of the approved themes of the research works of the Department of Medical Biology and Genetics “Morphofunctional and biochemical substantiation of the dysfunction of the neurosecretory structures of the brain and endocrine glands and hepatorenal system of rats at experimental pathology, in age aspect and ways of its correction (state registration number 0119U101346) and “Morphofunctional changes of the structures of the nervous and endocrine systems in different periods of the postnatal ontogenesis and biochemical mechanisms of the signal molecules metabolism, the state of oxidant and antioxidant systems under conditions of experimental pathologies and glutathione and melatonin effect (experimental investigation”) (state registration number 0124U002513).

Results and their discussion

Medial small cellular subnuclei of the hypothalamic ventricular nucleus. Using immunohistochemical techniques, positive staining was observed in the medial small cellular subnuclei of the hypothalamic preventricular nucleus as granules, different as to density and size, which were mostly concentrated on the periphery of the subnuclei under study. This, in its turn, is the evidence of the transmembrane location of melatonin 1A receptors (Fig. 1). We did not detect immunohistochemical staining of nuclei, the detected structures were stained exceptionally with hematoxylin and showed a typical morphological structure concerning neurons of the medial small cellular subnuclei of the hypothalamic preventricular nucleus. It was noteworthy, that using the data of the microdensitometry study at 14.00 compared to 2:00, a probable decrease in the optical density of immunohistochemical staining was detected in the medial small cellular subnuclei of the paraventricular nucleus, what we consider to be a decrease in the density of melatonin receptors (Table 1).

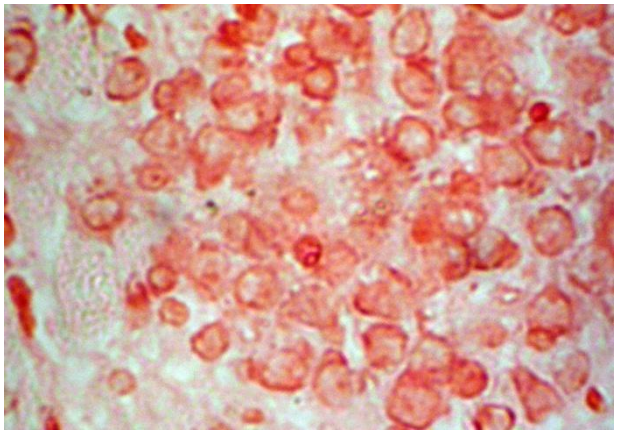

Fig. 1. Density of melatonin receptors 1A in neurons of the medial small cellular subnuclei of the paraventricular nucleus of the rats’ hypothalamus at 02.00. Vol.40x, Oc.10x.

Notes. Immunohistochemical technique with polyclonal antibodies to melatonin receptors 1A and streptavidin-biotin visualization system LSAB2 (peroxidase sign + diaminobenzidine). Additional staining of cell nuclei with Mayer's hematoxylin

Under conditions of constant darkness, the density of melatonin receptors 1A in the medial small cellular subnuclei of the paraventricular nucleus of the hypothalamus was characterized by stably high values with probably higher value during the night stage of observation (table).

Keeping animals under light exposure conditions resulted in a significant decrease ($p<0.001$) in the immunohistochemical density of melatonin 1A receptors in the medial small cellular subnuclei of the hypothalamic ventricular nucleus compared to both the control group and animals in which pineal hyperfunction was simulated, although the fluctuations of the index on average did not differ during the day.

Thus, if the density of melatonin 1A receptors in the neurons of the medial small cellular subnuclei of the hypothalamic ventricular nucleus of rats under the standard lighting regime was marked by clear daily fluctuations, then the change in lighting led to their expressed disturbance. Under conditions of constant lighting, the density of the structures under study is probably lower than under light deprivation.

Table 1

Optical staining density for melatonin receptors 1A in neurons of the paraventricular nucleus of the hypothalamus of rats at different photoperiod durations and melatonin introduction ($\bar{x} \pm S_{\bar{x}}$)

Hours of the day	Optical staining density (rel.un.of optical density)			
	LD (n=6)	LL (n=6)	DD (n=6)	LL+ melatonin (n=6)
Medial small-cellular subnuclei				
02.00	0,268±0,0021	0,188±0,0025	0,289±0,0022	0,252±0,0023
14.00	0,237±0,0020*	0,185±0,0023	0,278±0,0022*	0,229±0,0022*
Lateral large-cellular subnuclei				
02.00	0,270±0,0025	0,187±0,0021	0,292±0,0023	0,253±0,0026
14.00	0,248±0,0026*	0,186±0,0019	0,279±0,0021*	0,226±0,0021*

*Notes: LD – 12.00C:12.00T; LL – 24.00C:00T; DD 00C: 24.00T; n – number of animals; * – difference probability ($p<0.05$) in comparison with the previous time interval within the group*

With the object of correcting the density disorders of melatonin receptors 1A in the neurons of the medial small cell subnuclei of the hypothalamic ventricular nucleus, caused by prolonged exposure of rats to constant lighting, melatonin was used at a dose of 1,5 μg/kg of animal body weight. When using the drug, immunohistochemical analysis at 14.00 showed a probable increase in the optical density of the specific staining of the structures under study concerning to that in animals which did not receive melatonin injections against a background of light stress (table). If during light exposure the index constituted 0.188±0.0025 rel.un.of optical density at night (02.00) and 0.185±0.0023 rel.un.optical density during the daytime (14.00), then when melatonin was administered against a background of prolonged lighting, the optical density of the specific staining reached 0.252±0.0023 rel.un.optical density at 02.00 and 0.229±0.0022 optical density at 14.00, respectively. According to the Newman-Keuls criterion, the difference between the groups, the samples of which were taken for research both during the day and at night, is probable ($p<0.05$).

Lateral large cell subnuclei of the hypothalamic ventricular nucleus. The results of the optical density measurements of specific staining for melatonin receptors 1A in the lateral large cell subnuclei of the hypothalamic ventricular nucleus are presented in the table, according to the data of which, the highest density of melatonin receptors is observed at night, compared with the daytime indices. The averaged data of microdensitometric studies of the immunohistochemical density of melatonin receptors 1A in neurons of the lateral large cell subnuclei of the hypothalamic nucleus by keeping rats under conditions of constant darkness are also stably high at 02.00, and probably decrease in the daytime.

Unlike animals, kept in constant darkness, in rats that were under conditions of prolonged lighting, the number of neurons positively stained for melatonin receptors 1A of the lateral large cell subnuclei of the preventricular nucleus of the hypothalamus was probably lower. Its highest values were recorded at 02.00, when the index was 0.187±0.0021 rel.un. opt. density, and probably did not differ from that at 14.00. By means of comparing the obtained data of the optical density of specific staining for melatonin receptors 1A in neurons of the lateral large cell subnuclei of the preventricular nucleus of the rats' hypothalamus in different daily periods with modeling various light intensities, it became possible to ascertain the fact of a stably low index in the studied daily intervals in animals that were under prolonged light exposure, as well as a probable index increase in animals that were kept under light deprivation conditions (table).

Probable changes, caused by light stress, in the density of melatonin receptors 1A in neurons of the lateral large cell subnuclei of the hypothalamic preventricular nucleus of rats concerning the density of the receptors under study in animals that did not receive the drug against a background of light stress both at 14.00 and at 02.00 (table), were determined immunohistochemically by melatonin correction (1,5 mg/kg of animal body weight). Under such experimental conditions, a tendency to index normalization, which at night constituted 0.253±0.0026 rel.un. opt. density, and during the day it probably decreased being within the limits of - 0.226±0.0021 rel.un. opt. density, was observed.

Conclusions

1. The density of melatonin receptors 1A in neurons of the medial small-cell and lateral large-cell subnuclei of the preventricular nucleus of the hypothalamus of old rats is subjected to circadian organization. The highest density of receptors in secretory neurons of the paraventricular nucleus is observed at 02:00, and at 14:00 it probably decreases.
2. Photoperiod modification causes a marked desynchronization of daily fluctuations of the density under study. At prolonged exposure to light, in comparison with both the control index and that as under light deprivation, the optical density of the specific staining lower and is at 02.00: in neurons of medial small-cell subnuclei 0.188±0.0025rel.un.optical density, in neurons of lateral large-cell subnuclei – 0.187±0.0021 rel.un. optical density, and at 14.00 – 0.185±0.0023 and 0.186±0.0019 optical density units, respectively.
3. When using melatonin against a background of prolonged lighting, probable index increase concerning to such in old animals not given the drug against a background of light stress, with a tendency to its normalization was observed.

Prospects for scientific research

Henceforth, similar experiments to identify possible mechanisms of disturbances in the density of melatonin 1A receptors in the hypothalamic neurons of old rats, but

with a different light regimen for keeping animals, are projected to conduct.

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