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MELATONIN - AS THE PINEAL GLAND PRODUCT IN REGULATION OF PHYSIOLOGICAL FUNCTIONS OF THE ORGANISM

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Objective *- to investigate the pineal gland product - hormone melatonin in the regulation of physiological processes and body functions.*

Material and methods*. Experimental studies were conducted on white, sexually mature male rats. The first group (control) - intact rats; the second one - animals, subjected to acute immobilization stress; the third group - animals which were administered melatonin-based drugs before immobilization stress. In order to correct the renal functions impairment, the animals under study received exogenous vita-melatonin preparations (pharmaceutical preparation "Vita-melatonin", Kyiv vitamin plant, Kyiv), which was administered at a dose of 0.3 mg / kg body weight (1 tabl. contained 0.003g of melatonin, dissolved in 30 ml of isotonic sodium chloride solution) one-time intragastrically by means of a probe one hour before the immobilization stress in the evening.*

Results. *Melatonin use positively affects the function of the kidneys and reduces the negative effects of stress on the vascular-glomerular level. Despite the improvement in average daily diuresis levels, the concentration index of endogenous creatinine, relative reabsorption of water, the changed phase structure of rhythms was maintained. Moreover, in certain periods, the probable deviations of the parameters in comparison with the control values were recorded. Hyperazotemia, disturbance of the concentration function and proteinuria were retained, but these changes were significantly less than at immobilization stress without exogenous melatonin. Approximation of the rhythms' amplitude to control indices should be considered as a favorable prognostic sign.*

Melatonin protective effect was noted in violations of ion-regulating and acid-discharging kidney function. Positive changes were observed in the concentration of sodium ions in plasma, clearance of non-sodium water, proximal transport of sodium ions, pH of urine, excretion of titrated acids and ammonia. The inhibition of the processes of reabsorption of sodium ions during intensification of ammonia and acidogenesis was maintained.

Conclusions*. Thus, damages of the renal transport systems under the influence of immobilization stress are associated with organic changes in the epithelium of the renal tubules, on which melatonin produces protector effect.*

Ключові слова: *шишкоподібна залоза (епіфіз), мелатонін, фізіологічні функції.*

Клінічна та експериментальна патологія Т.17, №3 (65), Ч.2.-С.142-149.

МЕЛАТОНІН - ЯК ПРОДУКТ ШИШКОПОДІБНОЇ ЗАЛОЗИ В РЕГУЛЯЦІЇ ФІЗІОЛОГІЧНИХ ФУНКЦІЙ ОРГАНІЗМУ

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Мета роботи *- вивчити продукт шишкоподібної залози - гормон мелатонін у регуляції фізіологічних процесів та функцій організму.*

Матеріали і методи. *Експериментальні дослідження проведені на білих статевозрілих щурях-самцях. Перша група (контрольна) - інтактні щури; друга група - тварини, які піддавалися гострому іммобілізаційному стресу; третя група - тварини, яким уводили перед іммобілізаційним стресом препарати на основі мелатоніну. З метою корекції порушень функцій нирок піддослідні тварини отримували екзогенний препарати віта-мелатонін (фармацевтичний препарат "Віта-мелатонін", ЗАТ "Київський вітамінний завод", м. Київ), який уводили в дозі 0,3 мг/кг маси тіла (1 таблетка містила 0,003 г мелатоніну, її розчиняли в 30 мл ізотонічного розчину натрію хлориду) одноразово внутрішньошлунково через зонд у вечірній час за 1 год до іммобілізаційного стресу.*

Результати. *Використання мелатоніну позитивно впливає на функцію нирок і зменшує негативні ефекти стресу на судинно-клубочковому рівні. Незважаючи на покращання середньодобових рівнів діурезу, концентраційного індексу ендогенного креатиніну, відносної реабсорбції води, зберігалася змінена фазова структура ритмів. Більше того, в окремі періоди реєстрували вірогідні відхилення параметрів порівняно з контрольними значеннями. Зберігалися гіперазотемія, порушення концентраційної функції і протеїнурія, але ці зміни значно менші, ніж за іммобілізаційного стресу без екзогенного мелатоніну. Сприятливою прогнос-*

тичною ознакою слід вважати наближення амплітуди ритмів до контрольних показників. Протекторний ефект мелатоніну відмічали щодо порушень іонорегулювальної та кислотовидільної функцій нирок. Спостерігали позитивні зміни концентрації іонів натрію в плазмі, кліренсу безнатрієвої води, проксимального транспорта іонів натрію, pH сечі, екскреції кислот, що титруються та аміаку. Зберігалося пригнічення процесів реабсорбції іонів натрію при інтенсифікації амоніо- та ацидогенезу.

Висновки. *Пошкодження ниркових транспортних систем при впливі іммобілізаційного стресу пов'язано з органічними змінами епітелію ниркових канальців, на які мелатонін справляє протекторний ефект.*

МЕЛАТОНИН - КАК ПРОДУКТ ШИШКОВИДНОЙ ЖЕЛЕЗЫ В РЕГУЛЯЦИИ ФИЗИОЛОГИЧЕСКИХ ФУНКЦИЙ ОРГАНИЗМА

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Цель работы *-изучить продукт шишковидной железы - гормон мелатонин в регуляции физиологических процессов и функций организма.*

Материалы и методы. *Экспериментальные исследования проведены на белых половозрелых крысах-самцах. Первая группа (контрольная) - интактные крысы; вторая группа - животные, которые подвергались острому иммобилизационному стрессу; третья группа - животные, которым вводили перед иммобилизационном стрессом препараты на основе мелатонина. С целью коррекции нарушений функции почек подопытные животные получали экзогенный препараты вита-мелатонин (фармацевтический препарат "Вита-мелатонин", ЗАО "Киевский витаминный завод", г. Киев), вводили в дозе 0,3 мг / кг массы тела (1 таблетка содержала 0,003 г мелатонина, ее растворяли в 30 мл изотонического раствора натрия хлорида) однократно внутрижелудочно через зонд в вечернее время за 1 ч до иммобилизационного стресса.*

Результаты*. Использование мелатонина положительно влияет на функцию почек и уменьшает негативные эффекты стресса на сосудисто-клубочковой уровне. Несмотря на улучшение среднесуточных уровней диуреза, концентрационного индекса эндогенного креатинина, относительной реабсорбции воды, сохранялась изменена фазовая структура ритмов. Более того, в отдельные периоды регистрировали возможные отклонения параметров по сравнению с контрольными значениями. Хранились гиперазотемия, нарушение концентрационной функции и протеинурия, но эти изменения значительно меньше, чем за иммобилизационном стресса без экзогенного мелатонина. Благоприятной прогностическим признаком следует считать приближения амплитуды ритмов к контрольным показателям. Протекторный эффект мелатонина отмечали о нарушениях ионорегулювальной и кислотовидильной функции почек. Наблюдали положительные изменения концентрации ионов натрия в плазме, клиренса безнатриевои воды, проксимального транспорта ионов натрия, pH мочи, экскреции кислот, титруемых и аммиака. Сохранялось угнетение процессов реабсорбции ионов натрия при интенсификации амонио- и ацидогенез.*

Выводы. *Повреждения почечных транспортных систем при воздействии иммобилизационном стресса связано с органическими изменениями эпителия почечных канальцев, на которые мелатонин оказывает протекторный эффект.*

Ключевые слова: *шишковидная железа (эпифиз), мелатонин, физиологические функции.*

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Introduction

Photoperiodism is one of the main ecological factors on the bases of which rhythmics of the body activity is formed. Metabolism activity, breathing intensity, heart beating, diuresis etc., being the important condition of a living being adaptation to surroundings, are changing in alteration of day and night [6,18,30]. The pineal gland, which forms chronobiological functional block with suprachiasmatic nuclei of the hypothalamus and peripheral endocrine structures, is the main organizer of the twenty-four-hour periodism in the spinal animals according to photoperiodical changes in the environment [19, 20]. Brain epiphysis participation in circadian rhythms formation was detected in modulated situations with a change of photoperiod length or light regime inversion. [8, 19]. The pineal gland is considered as one of the central pacemakers, which has the endocrine properties [16, 23, 26].

Biochemical bases for adaptation of the organism are, in the first place, reactions of the endocrine system to specific characteristics of the natural geochemical and anthropogenic factors [1, 2, 21]. The pineal gland as the endocrine organ in the brain structure plays a particular role in the formation of the adaptive reactions, regulates a chain of processes important for life [11, 12]. This regulation is cyclic, therefore, in the opinion of many researchers, epiphysis is a regulator of "biological clock" in the organism [10, 20, 22].

Brain epiphysis correlates activity of the CNS and peripheral endocrine apparatus in changeable conditions of the environment depending upon photoperiod length. These effects are carried out, first of all, by means of the pineal gland secretion of the main hormone of indole nature - melatonin [5, 7, 8]. Melatonin level in the tissues of the organism clearly corresponds to the light intensity [9, 29]. It has been studied that lighting with intensity of 2000Lx during sleeping is suitable to inhibit melatonin synthesis and leads to different neuroendocrine disorders. Instead of, the evident bright lighting in length of a day increases melatonin night excretion and organism immune response, in this connection daily staying of a man under conditions of lighting with intensity of 500 Lx is used in the treatment of various sleep disturbances [1, 2, 10, 19]. Even separate light signal is enough for phase time displacement of melatonin secretion start [19, 25, 31].

Melatonin level in circulation begins to increase in the evening hours reaching maximum value to the middle of the night, and then decreases progressively to minimal values in the morning [10, 13, 27].

Melatonin content in the brain epiphysis and blood serum of the biological objects varies due to different stress action [18, 24, 33]. For example, gamma-irradiation leads to primary disappearance and in future to melatonin concentration increase in the brain epiphysis. Similar changes are marked at xenobiotic action [18, 28, 32].

Following melatonin introduction to epiphysisectomized animals sodium ions excretion and its filtration charge returns to normal, sodium ions reabsorption decreases in proximal nephron channel against a background of its concentration decrease in skeletal and cardiac muscles, hemispheres of the cerebral cortex and level increase in the liver, lungs, suprarenal glands [8, 19, 32].

Both internal and external desynchronization may be the cause of different pathological conditions, for example, while changing work regime, work in shifts, flights through some time zones which attend diseases of inner organs [3, 4]. Melatonin is used to decrease these negative symptoms. But there are warnings concerning prolonged administration of this hormone, since it may cause frequency increase of the malignant tumors of the lungs and lymphomas [3, 15].

At glomerulonephritis, complicated by chronic renal insufficiency, the range of phase-amplitude relations of the glomerular filtration rate narrows and displaces to later hours, but in later stages of chronic renal insufficiency the amplitude, on the contrary, increases [8, 10, 13, 14]. In chronic renal insufficiency acrophase of the sodium ions excretion displaces to the morning hour, mezor of rhythm reduces from 0.08 to 0.03 mmol/min, the amplitude of fluctuations decreases [8, 15, 21]. Amplitude and mezor rhythm of potassium ions excretion reduces in patients already on initial stages of chronic renal insufficiency, acrophase displaces to later hours [8, 20, 23]. Acrophase position and amplitude value of chronorhythms' excretion of the titrated acids and ammonia are kept in patients with chronic glomerulonephritis, but mesors of these rhythms decrease [5, 8, 10].

It has been established that daily rhythm of diuresis and ion regulative function of kidneys in rats is controlled by the pineal gland. Removal of this gland causes desynchronism of the renal activity, that is manifested by amplitude decrease of fluctuations, displacement of urinary excretion rhythm and potassium uresis from night to day period [8,19, 20].

At introduction of exogenous melatonin to the animal with removed epiphysis, hypersodiumuremia is observed, sodium ions excretion and its filtration charge increases during early terms following the operation, reabsorption of the given cation decreases, potassium ions excretion with urine is reduced [4, 8, 13, 19].

Intraperitoneal administration of exogenous melatonin can influence upon acid excretive function of the rat kidneys. These effects have secondary sodium-dependent character because of inhibition of sodium ions reabsorption in proximal nephron tubules and is realized due to disorder of the channel-tubules balance [8, 16, 25].

Hormones of the pineal gland have a wide spectrum of action and regulate the important physiological functions. Epiphysesectomy, or inhibition of the pineal gland function, decreases the animals' life span, while administration of exogenous melatonin and peptide preparations of the pineal gland to the rats prolongs it [2, 10, 20, 22].

Melatonin is involved in regulation of stressor reactions and adaptation of the organism in extreme conditions. It is known that anti-stressor melatonin action equally with chronobiologic mechanisms may be provided with hormone influence on stress-limiting and stress-realizing mechanisms of the brain. Involvement of GABA-ergic and dopaminergic mechanisms is only one of neurochemical components of melatonin anti-stress action [17, 18, 26].

Melatonin has been shown to possess anti-ulcerative action, stimulates prostaglandin E_2 synthesis with the stomach mucous and improves microcirculation [19, 20, 22]. The pineal gland indole role is known in the correction of the disorders of the endocrine system and metabolism, in the treatment of arterial hypertension, in coordination of chronorhythms of non-specific resistance, its positive effect has been detected at wound healing [22, 28].

Melatonin is considered not only as a messenger of the main endogenous rhythm, but as a corrector of this rhythm concerning cyclic phenomenon, which occur in the environment [14, 15, 25]. Spectrum of melatonin action is rather broad: it is considered to be one of the strongest endogenous antioxidant at lipid peroxidation [21, 24]. It stimulates the production of immunoglobulins and interleukins by leukocytes, which in its turn, influence upon its secretion. This hormone also inhibits proliferation of cells, makes weaker stress effects and realizes anti-stress action, synchronization of fluctuation processes in the body [13, 17, 27]. Melatonin as one of the powerful anti-oxidant of the organism, manifests neuroprotective and antiradical properties in vitro and in vivo [21, 32].

Sharp decrease of POL, when keeping rats under conditions of constant darkness, is confirmation of melatonin anti-oxidant action [5, 7, 32].

Long-term parental melatonin introduction positively

changed biochemical composition of the granulation-fibrous tissue of the extensive surgical wounds of male-rats in the process of healing. Investigation has shown that during the whole term of administration melatonin manifested protective effect, partially levelling changes in biochemical composition of the granulation-fibrous tissue, caused by stress situation [18, 30, 32].

The pineal gland is not the exclusive organ of melatonin synthesis. Cells, which synthesize melatonin and its basic precursor-serotonin, are located in gastrointestinal tract, subhepatic capsule, cortical layer of the kidneys, between cortical and cerebral zones of the adrenal glands, in paraganglia, gallbladder, ovaries, placenta, endometrium, [1, 3, 8, 10].

For some time past melatonin receptors in different organs are assiduously studied. Extrapineal melatonin can also act as type hormone, reaching distant target-cells by means of the blood flow. In various organs there are receptors to melatonin, which may control different hormonal and immunological functions [4, 6, 9, 29].

Receptors of melatonin are detected in nuclei and cell membrane, therefore, they are divided into nuclear and membranous. Nuclear receptors are present both the brain and tissues, which do not belong to the nervous system. Membranous receptors of melatonin predominate in the nervous tissue; they have high relationship with melatonin [2, 7, 10, 20, 22].

Thus, it should be noted the necessity of investigation of the peculiarities of chronorhythm reconstructions of the basic functions of the organism, caused by stress reaction. The results give the possibility to work out chronobiological criteria of early diagnostics of biochemical changes in kidneys, to improve time schemes of the therapeutic measures concerning diseases of various forms of the clinical course, which appear under conditions of stress, to determine their role in adaptation mechanisms of a human being to the environment and methods of prophylaxis using melatonin preparations [18, 10, 21, 22].

Objective - to investigate the pineal gland product - hormone melatonin in the regulation of physiological processes and body functions.

Results and their discussion

When carrying out the investigations the authors tried to elucidate the optimal period of exogenous melatonin administration for the purpose of correction of the mentioned disorders. It has been revealed that the indices of the main renal functions reached maximally the data of the intact animals under conditions of melatonin administration 1 hour before stress [18, 19].

The confirmation of it may be the data, obtained by Ye. B. Arushanian and co-authors, who showed in experiment, that melatonin, administeted to the animals 30 minutes to the stress by means of the method of the forced swimming, resulted in prolongation of the state of immobility and decrease of the latent period of the first immobilization appearance [5, 9, 10]. According to this index melatonin effect may be considered as distressogenous action, since the degree of immobilization weakening is taken as a criterion of anti-depressive activity [13, 14, 15]. Possibility of melatonin modulation influence upon the function of the brain receptor apparatuses, which take part in anti-depressants effects, is not excluded [19, 22, 22].

A number of authors studied melatonin anti-stress action. V.B. Shatylo, in particular, points-out that decreasing activity of the hypothalamus-hypophysial and sympathoadrenal systems, melatonin decreases initial phase of the stress reaction and may be used for correction of the increased stress reaction of the cardiovascular system during psychoemotional stress [2, 10]. Its positive influence upon the mechanism of neuroendocrine regulation is supplemented with anti-oxidant effect. Other researchers came to the same conclusion [17].

The pineal gland is an important element of the stress-limiting mechanisms, which are starting in response to the stress mobilization of hypothalamus-hypophysis-adrenocortical system. V.P. Pyshak, in particular, indicates that anti-stress effect of its indole melatonin is reached due to the whole chain of mechanisms (neurophysiological, chronobiological, endocrine, immune), among which changes in the hypothalamus of neuromediatory processes, first of all, GABA and dopaminergic, are considered to be the most significant [8, 19].

Investigations have shown that pre-stress melatonin administration causes changes of stress-reactivity of angiotensin-converted enzyme, which occur against a background of corticosteroids level decrease and may be confirmation of anti-stress melatonin activity [4, 6, 19].

The cited literature data are coordinated with the results obtained by us, which are evidence that immobilization stress disturbs the circadian organization of the renal function. The typical manifestations of these disturbances are: chronorhythms' inversion of absolute and relative diuresis with disturbance of sinusoidal character and bathyphase urine excretion in the evening; mezor of the concentrative index of endogenous creatinine veritably decreased; high amplitude of the circadian fluctuations of creatinin concentration in the blood plasma; mezor decrease of the glomerular filtration rate with low amplitude of the rhythm and displacement of its phase structure; mezor decrease of protein excretion, phase shifting of proteinuria structure; the rhythm of the relative water reabsorption with miniphase at 14.00 got inversive structure; high average daily level of standardized sodium ions' excretion against a background of low mezor of its filtrative charge; synphase of sodium ions excretion, acrophase of the rhythm occurred at 02.00; chronorhythm of sodium ions concentration in the blood plasma relatively its excretion was of anti-phase character; inversion of chronorhythms of the proximal and distal transport of sodium ions; concentration index of sodium ions probably increased; ammonium coefficient increased in comparison with the values of the intact animals; there was shifting of the urine acidity acro-phase to the evening hours; inversion of chronorhythms' excretion of the titrated acids and ammonia.

Conclusions

Melatonin is involved in the regulation of stress reaction and adaptation of the organism in the extreme conditions. Melatonin anti-stress action side by side with chronobiological mechanisms may be supplied with hormone influence on stress limiting and stress realizing mechanisms of the brain. Damage of the renal transport systems under the influence of immobilizing stress is connected with epithelium organic changes of the renal tubules, on which melatonin produces protective effect.

Prospects for the research

To study melatonin derivative products and their role in the regulation of the epiphysis influence on the development of pathological changes.

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