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MORPHO-FUNCTIONAL STATE OF RATS PANCREAS UNDER MELATONIN ADMINISTRATION DURING OBESITY DEVELOPMENT: CHRONOTHERAPEUTIC APPROACH

Overweight and obesity often cause some comorbidity like insulin resistance, diabetes type 2, cancer, cardio-vascular pathology etc. Pancreas is the important organ in carbohydrate metabolism and insulin signaling, that under obesity conditions undergo pathologic changes. For diminish adverse effects of obesity in the role of therapeutic agent is considered melatonin – pineal gland pleiotropic multifunctional molecule. In view of development precision medicine, which include processing personalized data of whole genome sequencing, microbiome, individual day/night regime etc., time selection of drug administration for maximize efficacy and minimize side effects to each patient in according of private organism circadian rhythm is the main goal of chronotherapy approach. The aim of our study was to determine morpho-functional state (morphology characteristic of exocrine and endocrine part; morphometric parameters: areas of pancreatic islets, acini and acinar cell nucleus) of pancreas in rats with high-calorie (high fat) diet-induced obesity after melatonin administration in determined time of the day (evening and morning). Melatonin was administered daily by gavage for 7 weeks in dose 30 mg/kg 1 h before lights-off (ZT11, evening) or 1 h after lights-on (ZT01, morning) rats with high-calorie diet (HCD). Rats with HCD had morbid changes in pancreas cells morphology of exocrine and endocrine part, which manifested in presence of macrophage and leukocyte infiltration of islets, vacuolization and lipid droplets in acinocytes cytoplasm, while areas of islets, acini and acinar cell nucleus decreased. Obese rats with melatonin administration demonstrate amelioration of HCD-associated changes in pancreas. Namely, in rats with development obesity melatonin administrations increased area of pancreatic islets in comparison to HCD group, moreover pancreas acini area reach control values. Also were observed difference between time-of-day interventions of melatonin on acinar cell nucleus area parameters: evening administration showed more strong action in increased to control level direction. Together, is suggesting about melatonin ameliorative role on morpho-functional state of pancreas exocrine and endocrine part under HCD-induced obesity conditions, additionally evening administration 1 h before light-off displayed more beneficial influence compared to morning.

Keywords: melatonin, obesity, chronobiology, pancreatic islets, high-fat diet, pancreatic acinar cells.

Introduction. Obesity is one of the major diseases in the modern world. It is a multifactorial disease associated with several metabolic disorders, including insulin resistance, hyperglycemia, dyslipidemia and high blood pressure, which exacerbate each other [1]. They increase the risk of cardiovascular disease and type 2 diabetes, and their combination is called metabolic syndrome. Factors of metabolic syndrome include dysglycemia, atherogenic dyslipidemia, insulin resistance, hypertension and, in fact, obesity [2].

Worldwide, about 3.4 million people die from obesity every year, which is more than from underweight at the same time [3]. For every 5-unit increase in BMI above 25 kg/m², overall mortality increases by 29 %, vascular pathology mortality by 41 %, and diabetes-related mortality by 210 % [4]. According to the World Health Organization (WHO), obesity in Europe affects between 20 % and 30 % of adults, while in Ukraine, obesity are harmed 16 % of men and 26 % of women, whereas among children and adolescents, obesity expanded by 11.1 % [5].

One of the organs most affected by obesity is the pancreas, while disorders in its work affect the whole body and cause various diseases. Obesity is accompanied by ectopic fat accumulation, which leads to pancreatic steatosis, which in combination with metabolic syndrome is called non-alcoholic fatty pancreas disease (NAFPD). It is also possible to replace acinar cells with adipocytes. NAFPD is accompanied by infiltration of organ tissues by adipocytes and can develop into nonalcoholic fatty steatopancreatitis (NASP). Ectopic fat-related oxidative stress and adipocyte-produced adipocytokines lead to inflammation and organ dysfunction [6]. All of this is likely to increase the risk of pancreatitis, pancreatic cancer and B-cell dysfunction. Studies in Europe and America indicate that obesity, accompanied by acute pancreatitis of different etiologies, promotes severe pancreatitis, increases the risk of complications and increases mortality [7].

Nowadays the problem of acute pancreatitis is one of the most complex and unresolved in modern pancreatology, which often linked with increased body mass index (BMI) and mediated through elevated triglycerides [8]. The incidence of acute pancreatitis according to WHO is 20-80 cases per 100,000 population per year. The severe form accounts for about 15 % of all cases of acute pancreatitis. In necrotic pancreatitis, the mortality rate reaches 20-40 %. High lethality is associated with excessive activation of proteolysis, severe endotoxemia, and purulent-necrotic complications caused by both the lesion of the pancreas itself and parapancreatic area [9].

Today, one of the remedies for correcting pancreatic function is melatonin (MT), a hormone that was isolated from the pineal gland in 1958 by Aaron Lerner, but the link between the pineal gland and carbohydrate metabolism was established 75 years ago [10]. Since then, many studies have tested the effects of melatonin on carbohydrate metabolism, blood glucose and insulin secretion, and many conflicting results have been obtained, although all animals have elevated blood levels of melatonin at night and decreased in the afternoon, the physiological processes may be different depending on the lifestyle and modes of administration. Although melatonin receptors have been found in the pancreas, the role of melatonin in the pancreas has not yet been fully established [11]. In addition, although many studies have been devoted to the antioxidant effect of melatonin and its metabolites, there are doubts about the efficacy of melatonin as an antioxidant at physiological concentrations [12].

Thus, the aim of our study was to evaluate influence of melatonin different time (morning and evening) administration on pancreas morpho-functional state in rats with high-calorie diet-induced obesity.

Materials and methods. White nonlinear male rats weighing 100-120 g were used in this study. The light cycle was 12-h light and 12-h darkness, with lights-off at 19:00 h (ZT12). All experiments on animals were carried out in

compliance with the international principles of the European Convention for the Protection of Vertebrate Animals used for experimental and other scientific purposes (European Convention, Strasburg, 1986), Article 26 of the Law of Ukraine "On the Protection of Animals from Cruelty" (No. 3447-IV, February 21, 2006) as well as all norms of bioethics and biological safety.

During the first week, all animals received standard rodent chow. On the 8th day, the animals were randomized into 2 groups: control animals received standard chow (15,27 kJ·g⁻¹) for 10 weeks and experimental rats received high-calorie diet (HCD) (28,71 kJ·g⁻¹) consisting of standard chow (60 %), lard (10 %), eggs (10 %), sugar (9 %), peanut (5 %), dry milk (5 %) and vegetable oil (1 %) [13]. Food and water were available ad libitum. To confirm the development of obesity the animals were weighed one times a week until the average body gain reached a significant difference of at least 30 % between the two groups and the respective animals were classified as having the normal body mass (Control) and those with development of obesity (HCD). Rats of HCD group were divided into two subgroups: one subgroup received MT (group HCD_{ZT01}) in the morning 1 hour after light-on; animals of the second subgroups obtained MT administrations 1 h before light-off (group HCD_{ZT11}). Thus, the experimental four subgroups are indicated below as: normal body mass (control), HCD, HCD_{ZT01}, HCD_{ZT11}.

Melatonin (Alcon Biosciences, USA) was administered daily by single peroral by gavage introductions for 7 wk (30 mg/kg). Melatonin treatment was begun at 6th week of study after obesity is developed.

On the last day of the experiment, the animals were decapitated, and then the pancreas was isolated.

Histological examination was performed to characterize the morphology and functional status of pancreas. Fragments of pancreas in the size of 1x1 cm were fixed in 4 % of paraformaldehyde in 0.1 M phosphate buffer for 72 hours, after which they were dehydrated and embedded into paraffin according to a standard procedure. From the paraffin blocks, 5 μm sections were performed and stained with Bemer's hematoxylin and eosin. Further examination of sections was performed using a light microscope BX41 (Olympus, Japan). Microphotographs were taken using the DP20 (Olympus, Japan) digital camera and the Quick-PHOTO MICRO software (Promicra, Czech Republic).

The cross-sectional area of the acinar cell nucleus and the pancreatic acini were used as criteria for assessing the morphology and functional status of the pancreas exocrine part; and the cross-sectional area of the pancreatic islets was used to evaluation the state of the pancreas endocrine part. All parameters were measured using the Image J software (National Institutes of Health, USA).

Statistical data analysis was performed using the Statistica 6.0 (Stat-Soft, USA) and Microsoft Excel 2010 software (Microsoft, USA). The distribution of values was estimated using Shapiro-Wilk W-test. Since the deviation of these values distribution of from the normality was minor, to evaluate the differences between the values we used Student's t-test with a posteriori Bonferroni test. The differences with probability of the null hypothesis $p < 0.05$ were considered significant. The obtained results are presented as the mean ± standard error of mean.

Results and discussion. During the experiment, morphological changes in the histological structure of the pan-

creas in a group which receive a high-calorie diet were recorded (**Fig. 1 A, B**). In the exocrine part of the pancreas, along with normal tightly packed acini containing acinocytes in which there is pronounced acidophilia on the apical part and basophilia on the basal part of the cell, containing a rounded or oval nucleus (**Fig. 1 C**); was appeared basophilic cells (**Fig. 1 A**, asterisk), that can be may be acinocytes with impaired mechanism of synthesis and excretion of enzymes (that characterize reduced to absent zymogen granules and interstitial fibrosis [14]), or possibly macrophages, the accumulation of which is often accompanied by inflammation [15]. Macrophage infiltration may accompany interleukin-1 β secretion and decreases insulin secretion [16]. In the cytoplasm of some acinar cells were indicated vacuolization (**Fig. 1 A**, arrow) with structures that resembles lamellar bodies and which appear during activation of autophagy process [17]. In some acinar cells were explored lipid microvesicular droplets in apical side (**Fig. 1 B**, arrowheads) that is evidenced about fatty dystrophy in exocrine part of pancreas [18]. Pancreas of groups that received melatonin (both HCD_{ZT01} and HCD_{ZT11}) mostly did not demonstrate acute pathologic changes (**Fig. 1 D**) in exocrine part of pancreas and resemble to morphology pancreas of control group. Distinguish features between HCD_{ZT01} and HCD_{ZT11} did not observe.

Besides was marked changes in endocrine part of pancreas under conditions of HCD (**Fig. 2 A**): in pancreatic islets were destroyed (that can be caused by apoptosis of β -islets cells with followed fibrosis [19]), in some cases were observed leukocytes infiltrate in peripheral part of islets (**Fig. 2 A** arrow), that may also include macrophage with stimulation of inflame [20]. While in control group (**Fig. 2 C**) nucleus in cells of pancreas islets were light with good visible nucleolus and heterochromatin, in HCD group nucleus were dark with low synthetic activity, that resulting in falling acidophilic features of cytoplasm (**Fig. 2 B** asterisk). Groups that received melatonin (both HCD_{ZT01} and HCD_{ZT11}) mostly did not demonstrate acute pathologic changes (**Fig. 2 D**) in endocrine part of pancreas and resemble to morphology control group. Distinguish features in morphology of pancreatic islets between HCD_{ZT01} and HCD_{ZT11} did not observe.

The changes we described in HCD group accord with data of other HCD obesity model within 3 and 6 months, namely: lesions of the endocrine part in which some pancreatic islets were fibrotic and disorganized, in the tissues of the pancreas were signs of inflammation, contained macrophages and lymphocytes [21].

The morphometric assay denote on negative influence of HCD on the pancreas. The average area of the pancreatic islets for the HCD group decreased significantly by 55 % in compared to control (**Fig. 3**). Reduction of islets was shown also in high fat diet [22] and that can impact on insulin signaling destructions. In the HCD_{ZT01} group with morning melatonin administration, the average area of pancreatic islets decreased by 35 % in compared to control group and increased by 45 % in compared to HCD group. In the HCD_{ZT11} group with evening melatonin administration, the average area of the islets decreased by 24 % in compared to control group and increased by 69 % in compared to HCD group. However, no significant difference between HCD_{ZT01} and HCD_{ZT11} groups in the areas of the pancreatic islets is observed.

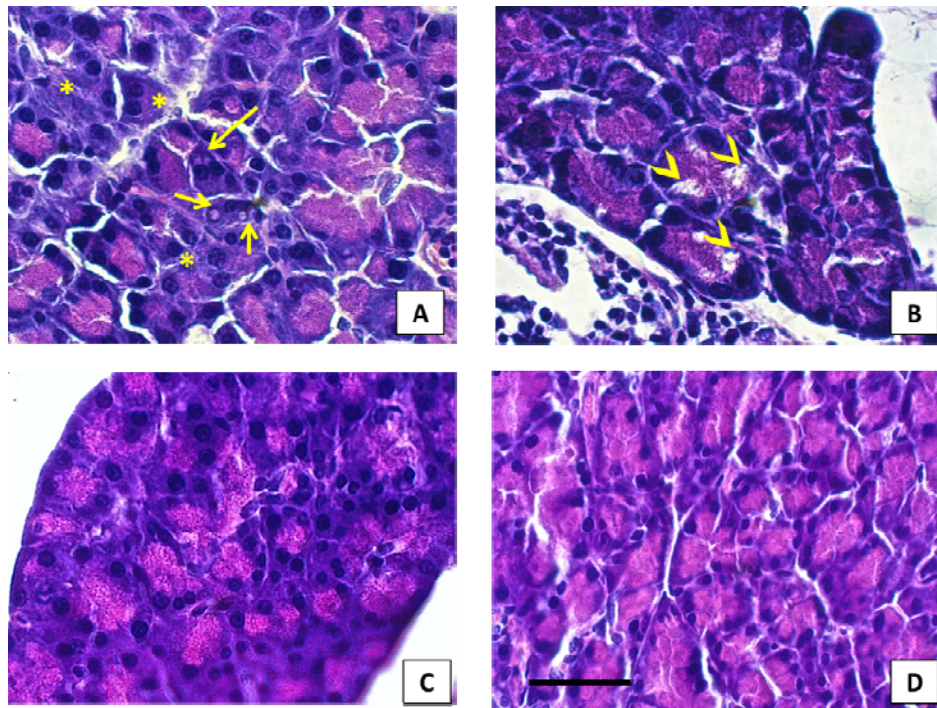


Fig. 1. Microphotographs of rats' pancreas exocrine part sections: A, B – HCD group; C – control group; D – HCD_{ZT11} group; hematoxylin-eosin staining; scale bar 30 μ m. Notes: arrow – cytoplasmic vacuolization of acinar cells, asterisk – basophilia of apical cytoplasmic part in acinar cells, arrowheads – microvesicular lipid droplet inclusions in the cytoplasm of acinar cells

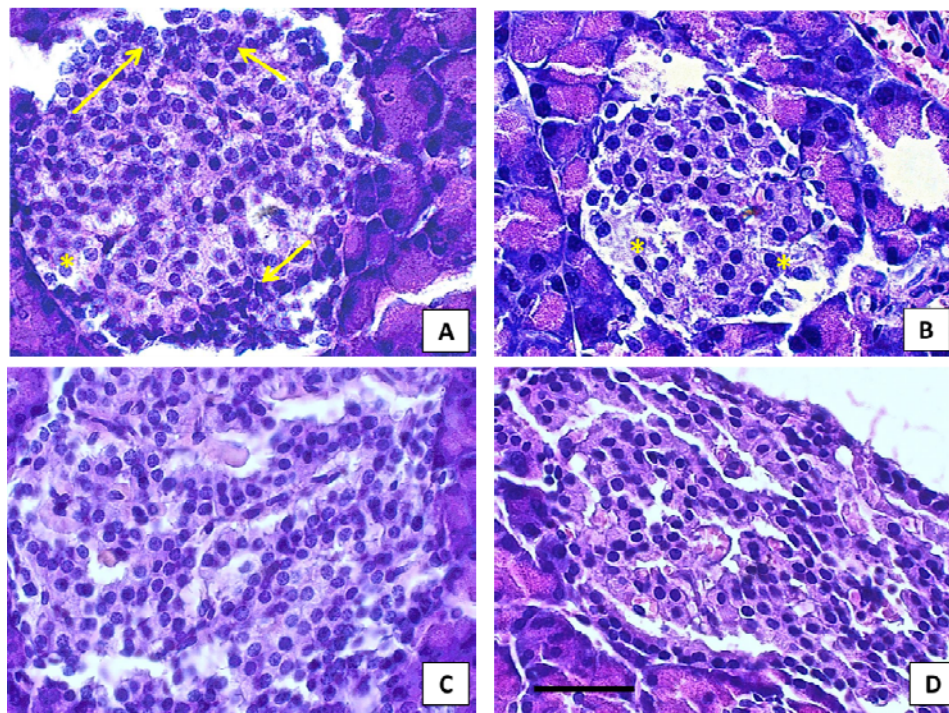


Fig. 2. Microphotographs of rats' pancreas endocrine part sections: A, B – HCD group; C – control group; D – HCD_{ZT11} group; hematoxylin-eosin staining; scale bar 30 μ m. Notes: arrow – leukocyte infiltration, asterisk – low acidophilic color of cytoplasm

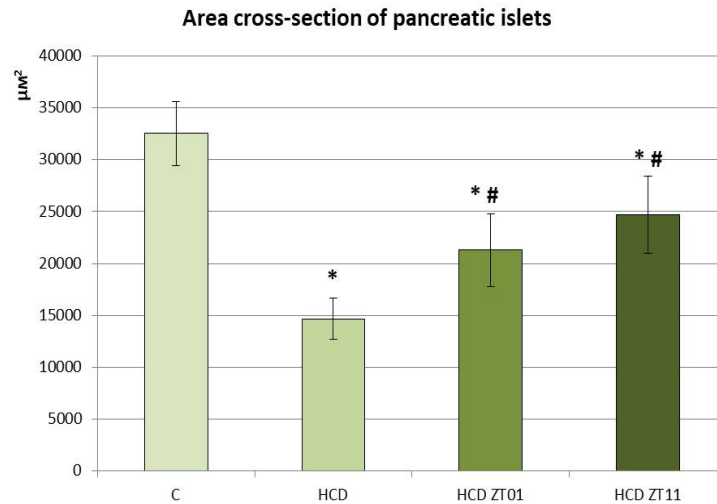


Fig. 3. The morphometric analysis data of the rats' pancreatic islets area.
C – control, HCD – obesity, HCD_{ZT01} – morning melatonin administration to rats with HCD, HCD_{ZT11} – evening melatonin administration to rats with HCD

Notes: * – a significant difference between the control and experimental groups, $p \leq 0.05$; # – a significant difference between the HCD and experimental groups, $p \leq 0.05$

In exocrine part of pancreas were analyzed cross-section areas of acini and acinar cell nucleus (Fig. 4). In the HCD group the acini area decreased by 30 % compared to control. At the same time, in the HCD_{ZT01} group with morning introduction of melatonin the acini area increased by 33 %, in HCD_{ZT11} increased by 47 % compared to HCD. Pancreatic acini area of melatonin treatment groups had reached control level and did not significant differ between each other group.

During obesity development area cross-section of acinar nucleus (Fig. 4) in HCD group decreased by 22 % compared to control. Decreasing acini areas as well as

acinocyte nucleus areas may indicate about diminish in protein synthesis in these cells. In the HCD_{ZT01} group, the nucleus area increased by 9 % compared to the HCD group, while compared to the control its level decreased by 21 %. In the HCD_{ZT11} group area of acinar nucleus increased by 21 % compared to the HCD group, but still by 11 % less than the corresponding parameter in the control group. In this case, a significant difference was found between the results obtained in the morning and evening administration: the average nucleus area at the HCD_{ZT11} group increased by 10 % than in the HCD_{ZT01}.

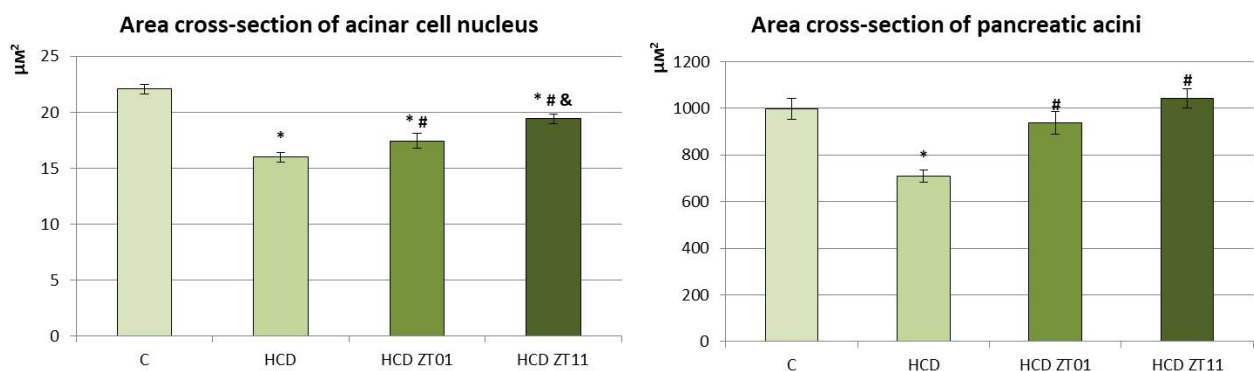


Fig. 4. The morphometric analysis data of the rats' pancreatic exocrine part. C – control, HCD – obesity, HCD_{ZT01} – morning melatonin administration to rats with HCD, HCD_{ZT11} – evening melatonin administration to rats with HCD.

Notes: * – a significant difference between the control and experimental groups, $p \leq 0.05$;

– a significant difference between the HCD and experimental groups, $p \leq 0.05$;

& – a significant difference between the HCD_{ZT01} and HCD_{ZT11}, $p \leq 0.05$

Thus, in the high-calorie diet group abnormal changes in the exocrine and endocrine parts of pancreas due to obesity development were detected. Our sections contained signs that obesity leads to ectopic accumulation of fat in cells, which is accompanied by inflammation. Obesity inflammation is observed in the liver, muscles, adipose tissue and pancreas. Obesity leads to organ infiltration by macrophages that produce proinflammatory cytokines [23]. Such macrophages were found in the morphological analysis of pancreas sections. A particular role in the onset of

inflammation is put on IL-1 β , which stimulates the production of a number of proinflammatory factors. IL-1 β itself is probably produced in response to the prolonged action of high concentrations of free fatty acids and glucose, which lead to cell damage and apoptosis. In addition, adipocytes also have the ability to synthesize cytokines and chemokines. Prolonged inflammation leads to a decrease in the pancreatic parenchyma mass and the fibrosis appearance [24], which we also observed on drugs.

Other animal studies have also shown that a high-fat diet leads to fibrosis. Obesity-induced insulin resistance, inflammation and lipotoxicity lead to pancreatic endocrine dysfunction and can cause decreasing β -cell number and thus diminished islet area [25]. Studies in mice have shown that a high-calorie diet with fat and carbohydrates leads to an increase in β -cell apoptosis, while a high-carbohydrate diet over the same period (12 weeks) moderate to an increase in β -cell mass and insulin secretion [26].

In humans, clinical studies suggest that there is a link between obesity and impaired endocrine pancreatic function, but most clinical studies do not find apparent abnormalities of exocrine pancreatic function in overweight individuals [27].

The melatonin usage in obesity development conditions partially retained the morpho-functional state of the pancreas. This is due to its nonspecific effects (antioxidant, anti-inflammatory) and specific effects on carbohydrate metabolism (MT1 and MT2 receptors have been detected in β -cells and α -cells). Also, with intraluminal administration, melatonin strongly stimulates the secretion of pancreatic enzymes, which is probably related to its effect on the digestive tract receptors [28].

Studies in mice using pinealectomy have shown that it leads to insulin resistance and leptin resistance. Exogenous administration of melatonin returned glucose metabolism back to normal level. In addition, a study in mice fed a high-fat diet showed that administration of melatonin corrected the reduced insulin sensitivity. In a mouse experiment with a genetic model of obesity, melatonin was shown to reduce inflammation and obesity-induced alteration of adipokine levels. Experiments indicate the lipolytic action of melatonin, which is achieved by stimulating the sympathetic nervous system [29]. Melatonin is known as an insulin synthesis inhibitor that can protect β -cells from damage by over-insulin synthesis during obesity.

A study in pigs with acute pancreatitis showed that the group receiving melatonin had less pronounced acinar and fat necrosis [30]. There are experiments that suggest the possibility of mitigating induced hyperglycemia obesity through the use of melatonin. This study showed the detrimental effect of smoking on the pancreas, which manifested in the reduction of pancreatic islets. Melatonin in this study reduced inflammation and apoptosis levels β -cells, improved the status and function of β -cells, and also increase insulin secretion [31].

Thus, the results of this experiment do not contradict the results of such experiments except those where a high carbohydrate diet was used.

Also in this experiment, a significant difference in the cross-sectional area of acinocyte nuclei was detected, depending on the time of melatonin administration. In the study of other parameters with the evening administration of melatonin, the results obtained were also closer to those in the control group. This difference may be related to the circadian rhythm of the body. Circadian rhythm is controlled at the level of the body – the pacemaker and the molecular clock at the cellular level. The central mammalian pacemaker is the suprachiasmatic nucleus (SCN) of the hypothalamus, and there are also peripheral pacemakers. The pacemaker is guided by an auto-transcriptional / translational feedback loop provided by clock genes. Interestingly, the pancreas has its own pacemaker rhythm. Thus, although insulin and glucagon secretion are dependent on food intake, experiments have shown the existence of circadian rhythm in their levels [32]. The main regulators of

circadian rhythm are CLOCK and BMAL1, they form a heterodimer and bind to an enhancer that regulates the expression of rhythm-related PER and CRY genes. The heterodimer formed by PER and CRY is directed to the nucleus, where it inhibits the expression of CLOCK and BMAL1. In β -cells of rats with knockout BMAL1, insulin levels are lower, suggesting that these genes are linked to carbohydrate metabolism [33].

SCN affect the synthesis of melatonin, and melatonin, in turn, regulates the functions of SCN, especially at dawn and at dusk. This is done at the expense of MT1 and MT2. There is evidence that the density of these receptors has a circadian rhythm: there are studies showing an increase in the density of MT1 receptors in SCN during dusk [34].

Melatonin exerts its specific effect on cells via MT1 and MT2 receptors. Thought MT2 receptors melatonin mediates the effect on insulin secretion with the activation of phospholipase C. MT2 inhibition experiments have shown a decrease in the effect of melatonin on insulin secretion. MT1 inhibition showed no such effect. There is evidence that MT2 receptors are more represented in β -cells and MT1 in α -cells [34].

Conclusions. Thus, it has been established that obesity induced high-calorie diet leads to significant changes in the morphological structure of pancreas exocrine and endocrine part. It has been shown that daily administration of melatonin in a dose of 30 mg / kg for 7 weeks to obese rats leads to improvement of the pancreas morpho-functional state. Observed a tendency of greater efficiency during evening melatonin administration more (1 hour before light-off) than morning (shown significant difference in area of acinar cell nucleus, and other parameters save this direction).

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МОРФОФУНКЦІОНАЛЬНИЙ СТАН ПІДШЛУНКОВОЇ ЗАЛОЗИ ЩУРІВ ПРИ ВВЕДЕННІ МЕЛАТОНІНУ ПІД ЧАС РОЗВИТКУ ОЖИРІННЯ: ХРОНОТЕРАПЕВТИЧНИЙ ПІДХІД

Зайва вага та ожиріння часто викликають такі супутні хвороби, як інсулінорезистентність, діабет другого типу, рак, серцево-судинні патології тощо. Підшлункова залоза грає важливу роль для вуглеводного обміну та сигнальних шляхів інсуліну, що в умовах ожиріння зазнають патологічних змін. Для зменшення несприятливих наслідків ожиріння в ролі терапевтичного агента розглядається мелатонін – багатофункціональний гормон епіфіза. З огляду на розвиток точної медицини, яка включає обробку персональних даних про послідовність геному організму, мікробіому, індивідуальний режим дня/ночі тощо, підбір часу прийому ліків для максимальної ефективності та мінімізації побічних ефектів для кожного пацієнта відповідно до циркадного ритму індивідуального організму становить основну мету у хронотерапевтичному підході. Тому метою нашого дослідження було визначення морфофункціонального стану (зміни структури клітин екзо- та ендокринної частин; морфометричні параметри: площі поперечного перерізу острівців Лангерганса, ацинусів та ядер ацинарних клітин) підшлункової залози у щурів з ожирінням, індукованим висококалорійною (з високим вмістом жиру) дієтою, після введення мелатоніну у визначений час доби (увечері або вранці). Мелатонін вводили щоденно протягом 7 тижнів дозою 30 мг/кг за 1 год до вимкнення світла (ZT11, увечері) або 1 год після включення світла (ZT01, уранці) щурам, які перебували на висококалорійній дієті (ВКД). Щури із ВКД мали патологічні зміни в будові клітин підшлункової залози екзо- та ендокринної частин, що виявлялись у наявності макрофагів, лейкоцитарної інфільтрації острівців, вакуолізації та ліпідних крапель у цитоплазмі ациноцитів; у той же час розміри площі поперечного перерізу острівців, ацинусів та ядер ацинарних клітин зменшувалися. Щури з ожирінням, яким вводили мелатонін, демонстрували зменшення вияву патологічних змін, пов'язаних із впливом ВКД на підшлункову залозу. А саме, збільшилась площа острівців підшлункової залози порівняно з групою ВКД; крім того, площа ацинусів підшлункової залози досягла контрольних значень. Виявили різницю між ранковим і вечірнім введенням мелатоніну за параметрами площі ядер ациноцитів: вечірнє введення виявляло більш ефективну дію в досягненні контрольного рівня. У сукупності мелатонін чинить амеліоративну дію на морфофункціональний стан екзо- та ендокринної частин підшлункової залози в умовах розвитку ожиріння, спричиненого ВКД. Причому після вечірнього введення мелатоніну (за 1 год до вимкнення світла) спостерігається краща тенденція до відновлення змінених параметрів підшлункової залози до контрольного рівня порівняно з ранковим.

Ключові слова: мелатонін, ожиріння, хронобіологія, острівці Лангерганса, висококалорійна дієта, ацинарні клітини підшлункової залози.

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МОРФОФУНКЦИОНАЛЬНОЕ СОСТОЯНИЕ ПОДЖЕЛУДОЧНОЙ ЖЕЛЕЗЫ КРЫС ПРИ ВВЕДЕНИИ МЕЛАТОНИНА ПРИ РАЗВИТИИ ОЖИРЕНИЯ: ХРОНОТЕРАПЕВТИЧЕСКИЙ ПОДХОД

Лишний вес и ожирение часто вызывают такие сопутствующие болезни, как инсулинорезистентность, диабет второго типа, рак, сердечно-сосудистые патологии и т. п. Поджелудочная железа играет важную роль для углеводного обмена и сигнальных путей инсулина, которые в условиях ожирения испытывают патологические изменения. Для уменьшения неблагоприятных последствий ожирения в роли терапевтического агента рассматривается мелатонин – многофункциональный гормон эпифиза. Учитывая развитие точной медицины, которая включает обработку персональных данных о последовательности генома организма, микробиома, индивидуальный режим дня/ночи и т. п., подбор времени приема лекарств для максимальной эффективности и минимизации побочных эффектов для каждого пациента в соответствии с циркадным ритмом индивидуального организма составляет основную цель при хронотерапевтическом подходе. Поэтому целью нашего исследования было определение морфофункционального состояния (изменения структуры клеток экзо- и эндокринной частей; морфометрические параметры: площади поперечного сечения островков Лангерганса, ацинусов и ядер ацинарных клеток) поджелудочной железы у крыс с ожирением, индуцированным высококалорийной (с высоким содержанием жира) диетой, после введения мелатонина в определенное время суток (вечером или утром). Мелатонин вводили ежедневно в течение 7 недель в дозе 30 мг/кг за 1 ч до выключения света (ZT11, вечером) или 1 ч после включения света (ZT01, утром) крысам, которые находились на высококалорийной диете (ВКД). Крысы с ВКД имели патологические изменения в структуре клеток поджелудочной железы экзо- и эндокринной частей, которые проявлялись в наличии макрофагов, лейкоцитарной инфильтрации островков, вакуолизации и липидных капель в цитоплазме ациноцитов; в то же время морфометрические данные площади поперечного сечения островков, ацинусов и ядер ацинарных клеток уменьшались. Крысы с ожирением, которым вводили мелатонин, демонстрировали уменьшение наступления патологических изменений, связанных с влиянием ВКД в поджелудочной железе. В частности, увеличилась площадь островков поджелудочной железы по сравнению с группой ВКД; кроме того, площадь ацинусов поджелудочной железы достигала контрольных значений. Обнаружили разницу между утренним и вечерним введением мелатонина по параметрам площади ядер ациноцитов: вечернее введение имело более эффективное действие в достижении контрольного уровня. В совокупности мелатонин оказывает амелиоративное действие на морфофункциональное состояние экзо- и эндокринной частей поджелудочной железы в условиях развития ожирения, вызванного ВКД. Причем после вечернего введения мелатонина (за 1 ч до выключения света) наблюдается лучшая тенденция к восстановлению измененных параметров поджелудочной железы до контрольного уровня по сравнению с утренним введением.

Ключевые слова: мелатонин, ожирение, хронобиология, островки Лангерганса, высококалорийная диета, ацинарные клетки поджелудочной железы.