EFFECT OF MELATONIN DIFFERENT TIME ADMINISTRATION ON THE DEVELOPMENT OF DIET-INDUCED OBESITY IN RATS

**Introduction.** Overweight and obesity have become major global public health problems. Worldwide, the proportion of adults with a body mass index (BMI) of 25 kg/m² or greater increased from 28.8% to 36.9% in men, and from 29.8% to 38.0% in women between 1980 and 2013 [1]. According to the official data of the WHO Bulletin published in May 2017, in 2014 year the nearly 2 billion adults worldwide are overweight and, of these, more than half a billion were obese [2]. Increasing evidence shows that obesity is associated with inflammatory and oxidative stress responses, which cause chronic disturbances including type 2 diabetes [3], cardiovascular disease [4], dyslipidemia, cancers [5], and other disease. The drivers of the obesity epidemic have been much debated [6]. An increased food energy supply and the globalization of the food supply, increasing the availability of obesogenic ultra-processed foods, are arguments for a predominant driver of population weight gain [7]. In the other hand, the involvement of both the behavioral aspects, such as calorie-rich diet, low physical activity and sleep deprivation, and the intrinsic factors, including adipose tissue deregulation, chronic inflammation, oxidative stress, and chronodisruption, has been identified.

Melatonin, the neurohormone of the pineal gland that transduces environmental information, especially about the photoperiod, to regulate and reset circadian rhythms [8]. This signal molecule involve in the measurement of daylength (because pineal melatonin synthesis and release are uniquely elevated at night, it is referred to as the chemical expression of darkness) for seasonal timing of reproduction, energy metabolism, thermoregulation and behavior in mammals [9]. In the latter, melatonin is known to affect body mass, adiposity, inflammation state, and both energy intake and expenditure [10, 11]. These effects may influence to the obesity development [12]. Especially, deficiency of melatonin (one of the consequences of sleep deprivation), that may rely on circadian dysruption of leptin and adiponectin secretion, has also been demonstrated to correlate with obesity [13].

Chronopharmacological studies show that drug effects may vary according to the time of administration [14]. These differences are mainly due to circadian variations in multiple physiological variables, such as blood flow and binding to plasma proteins that influence drug's absorption, distribution, metabolism or elimination [15]. In the case of melatonin, it is worth noting that, although many variables have been reported to influence its pharmacokinetics among them there is circadian time regulation [16]. The influence of the time of day on the effects of oral melatonin are important not only for circadian studies [17] but also for metabolism studies since, melatonin has different effects on glucose tolerance between day and night [18]. When melatonin levels are highest (during the hours of darkness), the affinity of melatonin for its receptor, total binding and the expression of melatonin receptor mRNA are lowest. In addition, when cultured or recombinant cells expressing melatonin receptors are exposed to melatonin chronically, the potency of melatonin at melatonin receptors decreases perhaps due to an uncoupling of the receptor from its effector, due to receptor internalization and/or due to receptor down-regulation [19, 20, 21]. However, when melatonin levels are lowest (during the hours of daylight), the affinity of melatonin for binding, total binding and the expression of melatonin receptor mRNA are highest [22].

Despite the large number of scientific papers devoted to studying melatonin for the treatment and prevention of obesity [10, 11, 12, 13], we still lack knowledge on the use of this signal molecule, since different doses, duration, route and time of administration were taken in the researches. This dependence is due to the different sensitivity (density, affinity) of melatonin receptors throughout the day [23], but the mechanism of such regulation is still completely unclear [24].

The aim was to study body mass and food consumption changes on the development of rat high-calorie diet-induced obesity after melatonin use and perform comparative study the treatment efficacy of melatonin evening (1 hour before light-off) vs morning administration (1 hour after light-on) for the prevention and treatment of development 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. 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, Strasbourg, 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 8h day, the animals were randomized into 2 groups: control animals received standard chow (3,81 kcal/g) for 10 weeks and experimental rats received high-calorie diet (5,35 kcal/g) consisting of standard chow (60%), pork fat (10%), eggs (10%), sugar (9%), peanut (5%), dry milk (5%) and vegetable oil (1%) [25]. 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. They were then divided into 6 group according to table 1.

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Table 1. Characteristics of animals experimental groups

| №  | Group name | Diet type | Melatonin treatment |
|----|------------|-----------|---------------------|
| 1  | Control (C) | Standard  | –                   |
| 2  | HCD        | High-calorie | –                  |
| 3  | M ZT01     | Standard  | 1 h after lights-on |
| 4  | M ZT11     | Standard  | 1 h before lights-off |
| 5  | HCD ZT01   | High-calorie | 1 h after lights-on |
| 6  | HCD ZT11   | High-calorie | 1 h before lights-off |

Melatonin (Alcon Biosciences, USA) was administered daily by gavage for 7 wk (30 mg/kg) either 1 h after lights-on (Zeitgeber time (ZT) 1) or 1 h before lights-off (ZT11) (Fig. 1). Melatonin treatment was began at 6th week of study after obesity is developed.

Food and water consumption were measured daily at the same time (09:00 to 10:00 h) and body weights were determined once a week. Body weight gain, relative daily food (kcal/day/g body weight) and relative daily water consumption (ml/day/g body weight) was determined for each rat. Body length was measured; body mass index (BMI) (the ratio of body weight (kg) of rats to the square of the body length (m²)) and Lee obesity index (the ratio of cube root of body weight (g) by nasoanal length (cm) and multiplying the result by 1000 [26]) were also calculated. The epididymal, retroperitoneal, perirenal fat pads were dissected and immediately weighed.

The statistical analysis of the results obtained was conducted using the Statistica 6.0 (StatSoft, USA) and Microsoft Excel 2010 (Microsoft, USA) software. Normality of data distribution was determined by the Shapiro-Wilks criterion. To assess the validity of the revealed changes, parametric (Student t-test for two-samples) and non-parametric (Mann-Whitney U-test for the independent groups) methods of variation statistics were used, the difference was significant at \( p < 0.05 \). The obtained results are presented as M ± SEM (mean ± standard error of mean).

Results and discussion.

To establish the obesity model, animals were fed HCD until there was a minimum difference of 30% body weight gain between rats fed HCD compared with those who were fed standard diet. As soon as this difference reached significance\( (p < 0.05) \), parts of HCD and standard diet fed rats were treated with melatonin either 1 h after lights-on (ZT1) or 1 h before lights-off (ZT11). The baseline information of body weight, related visceral fat weight, body mass index, and Lee index of experimental animals are presented on the table 2.

Table 2. Body weight gain, body mass index, Lee index and visceral fat weight of experimental animals

| Parameter                | Control | HCD | M ZT01 | M ZT11 | HCD ZT01 | HCD ZT11 |
|--------------------------|---------|-----|--------|--------|----------|----------|
| Weight gain (%)          | 195 ± 23| 271 ± 17*| 238 ± 16*| 207 ± 23*| 254 ± 25| 248 ± 26 |
| Body mass index (kg/m²)  | 6.12 ± 0.29 | 6.87 ± 0.23* | 6.12 ± 0.19* | 6.24 ± 0.05* | 6.44 ± 0.09 | 6.41 ± 0.04 |
| Lee index                | 288 ± 5  | 309 ± 3*  | 292 ± 4*  | 293 ± 2*  | 297 ± 1*  | 295 ± 3*  |
| Visceral fat weight (%)  | 1.78 ± 0.03 | 2.93 ± 0.31* | 0.92 ± 0.09* | 0.94 ± 0.23* | 1.81 ± 0.14* | 1.59 ± 0.18* |

Data are presented as the M ± SEM;
* \( p < 0.05 \) compared with control value,
# \( p < 0.05 \) compared with HCD.

The weight gain, BMI and Lee index in rats received standard chow, which administrated melatonin (M ZT01 and M ZT11), were not significantly different compared with control group, but the level of visceral fat weight was decrease\( (p < 0.05) \) in M ZT01 by 48% and in M ZT11 by 47%. However, the data in literature about melatonin influence on body weight in rats with type of diet are disputed: was shown decrease (continuously in drinking water for 12 and 24 weeks in dose 0.4 μg/mL [27], or for 9 weeks in dose 25 μg/mL [28], or for 3 and 6 weeks in dose 4 mg/kg/day [29]) or no effect (intrapitoneal injection for 6 months at 09:00 hr in dose 3 mg/kg/day [30], or for 2 weeks at 07:00 hr in dose 1 and 10 mg/kg/day [31], or for 5 weeks at 18:00 hr in dose 10 mg/kg/day [32], or continuously in drinking water for 10 weeks in dose 25 μg/mL [33], or for 8 weeks in dose 100 mg/kg/day [34]). In our study reduce in visceral fat weight in the absence of significant differences in food intake (data not shown) are worth exploring. A key piece of evidence in this regard is the observation that melatonin plays a role in seasonal changes in adiposity by increasing the activity of the sympathetic nervous system innervating white fat which leads to lipolysis [35].

The weight gain and BMI in HCD ZT01 and HCD ZT11 groups take intermediate value: there no significant difference
compare both to control and HCD group. If we pay attention to dynamics of weight gain (Fig. 2), all this data means that melatonin have influence to body mass changes and tendency to decrease weight gain during development of obesity. After 1 weeks of melatonin administration (on the 7th and 8th weeks of experiment) the weight gain of HCD ZT01 and HCD ZT11 groups begin stop growing and this tendency was maintained during following final 5 weeks (decreases in HCD ZT01 by 6% and in HCD ZT11 by 8% groups in relation to HCD, but still increased by 30% and 27% in HCD ZT01 and HCD ZT11 respectively in relation to control, to note HCD weight gain was higher by 40% than control).

Surprisingly, we observed significant difference in weight gain rate (Fig. 3 A, B). At 2nd and 3rd weeks after melatonin treatment (8th and 9th weeks of experiment) the weight gain rate were reduced both in HCD ZT01 by 50% and 29%, in HCD ZT11 by 38% and 67% ($p < 0.05$ compared with HCD). Lower values in HCD ZT01 at 1st weeks melatonin use (by 73% $p < 0.05$ compared with HCD) we explain the stress action under first week of morning administration by gavage, because the same raise we mark in M ZT01 by 62% ($p < 0.05$ compared with control). Anyway, except 1st week melatonin effect on weight gain rate in M ZT01 and M ZT11 groups was without significant difference throughout the experiment in compared with control (data not shown).
The following 4th and 6th weeks (10th and 12th weeks of all experiment) we found reduce value of this parameter in HCD, HCD ZT01 and HCD ZT11 groups to control level due to low quality of hight-fat chow (this points is outpoints).

The next 5th and 7th weeks (11th and 13th weeks of all experiment) the weight gain rate in HCD ZT11 continue loss to control values (by 72% and 57%, \( p < 0.05 \) compared with HCD), while in HCD ZT01 studied parameter did not significantly differ from HCD group.

![Graph of weight gain rate](image)

**Fig. 3 B. Dynamics of weight gain rate during evening melatonin treatment**

\# – HCD ZT11 \( p < 0.05 \) compared with HCD.

However, the average index of weight gain rate (Fig. 4) during last 6 weeks of experiment show decrease only in HCD ZT11 by 48% (\( p < 0.05 \) compared with HCD), changes in HCD ZT01 was insignificant (also average index of

![Graph of weight gain rate](image)

**Fig. 4. Effect of melatonin on weight gain rate during last 6 weeks of study**

\* – \( p < 0.05 \) compared with control value, \# \( p < 0.05 \) compared with HCD.

![Graph of food consumption](image)

**Fig. 5. Effect of melatonin treatment on relative daily food consumption**

However, the average index of weight gain rate (Fig. 4) during last 6 weeks of experiment show decrease only in HCD ZT11 by 48% (\( p < 0.05 \) compared with HCD), changes in HCD ZT01 was insignificant (also average index of
weight gain rate was in HCD elevated by 60% in compare with control (p < 0.05)). These data may be suggest about more efficient influence on the body weight gain rate by melatonin evening dose.

The information about Lee index and visceral fat weight also provide that melatonin ameliorated body mass dynamic under obesity development (Table 2). According to obtained results we have revealed an increase Lee index of HCD group by 7% (p < 0.05, 309 vs 288) compared with control rats. Study shown that Lee index in HCD ZT01 and HCD ZT11 decrease by 4% and by 4,5% respectively (p < 0.05) compared with HCD (297, 295 vs 309), and were similiary to control level after 7 weeks of melatonin treatment. The values of relative visceral fat weight also indicate efficient action of melatonin application on body mass under hight-calorie diet condition. The index of studied parameter in HCD attained values by 64% higher than controls. After melatonin use in HCD ZT01 and HCD ZT11 the relative visceral fat weight have fall to control level, at the same time it was decrease by 38% and 46% as compared with HCD group.

Interestingly, the changes associated with body mass (weight gain, weight gain rate, BMI, Lee index, visceral fat) happen independly of food and water consumption (Fig. 5, 6). As shown the control group consumed an average of 0.247±0.002 kcal/g of standard chow per day. The HCD rats ate an average of 0.337 ± 0.006 kcal/g of high-calorie food, which higher (strongly marked hyperphagia)by 37% (p< 0.05) than control rats. However, the rats in HCD ZT01 and HCD ZT11 ate an average of 0.327 ± 0.005 kcal/g and 0.347 ± 0.006 kcal/g of feed accordingly, which actually does not differ from the values of the HCD group, but elevated by 32% and 40% than control (p< 0.05). The relative daily food consumption in M ZT01 and M ZT11 were similar to control values and did not different statistically (0.258 ± 0.005 and 0.245 ± 0.003).

Studies have found that HCD rats consumed an average of 32.2 ± 0.4 ml/g of water per day, which is lower by 17% (p < 0.05), whereas control group drink 38.9 ± ± 0.8 ml/g. The relative daily water consumption in HCD ZT01 and HCD ZT11 were lower (p< 0.05) by 22% (30 ± ±0.6 ml/g) and by 14% (33.4 ± 0.7 ml/g) than the control group and did not differ from HCD group values. Melatonin administration significantly did not affect water consumption in M ZT01 (39.3 ± 0.9 ml/g) and M ZT11 (39.3 ± 0.6 ml/g).

This data in agreement with other researches: after melatonin treatment (continuously in drinking water for 8 weeks in dose 100 mg/kg/day) was demonstrated significance decrease visceral fat weight in obese (ob/ob) mice, while weight gain have intermediate position compare to control and obese animals [36]. But, on the other hand, under condition of HCD the concomitant administration (continuously in drinking water) of melatonin significantly attenuated a body weight increase without affecting chow or water consumption [33, 11, 37]. These data indicate that melatonin have other mechanisms to influence on body weight – stimulates the appearance of beige adipocytes (mixed type) in white adipose tissue [38] (which are contribute to the loss of excess accumulated triglycerides due to heat production); normalizes circadian secretion of adipokins [39]; shows anti-inflammatory [40] and antioxidant properties [41]; involvement in the regulation of appetite and intake of food through the influence on the hypothalamus nucleus [42]. Except intermediate and lower level of weight gain after melatonin use, there are information about "no effect" – in this studies was use reduce dose or period of administration [31, 29] (but also was shown visceral fat weight decreased), or another route of administration [43, 44].

A limitation of this study may be that no significative difference in HCD body weight gain was seen after 7 weeks of melatonin treatment; a longer duration of treatment may be needed to elicit such improvement or increased rats numbers in groups. Moreover, probably muscle weight gain would be interesting, since it have been shown raise in muscle Ferets diameters after melatonin use, which may also make contribution in body weight [45].

In the light of chronobiological question time of administration, our data suggest that evening melatonin administration improve visceral fat and body weight parameters more rapidly then morning. We hypothesized that morning dose may prolong night melatonin secretion peak to support its highest level for longer time, while evening dose was intended to raise endogenous night peak. However, weight gain, BMI, Lee index and visceral fat weight are lower and have more stronger expressed difference in HCD ZT11 then in HCD ZT01. Previous study shown the same results: melatonin effects on body weight in a model of overweight were possibly time dependent – the first melatonin administration (ZT 04) was less efficient than in ZT 11 (also reduces weight gain) [46]. Subcutaneous (or intraperitoneal) injection 2–3 h before lights-off decreased body weight and visceral fat too under influence middle dose of melatonin (1 or 4 mg/kg/day for 4 or 8 weeks) during developmental obesity [47, 48] and besides intra-
peritoneal injection in the morning at the same dose have no effect to body weight [31].

Conclusions. The application of melatonin by systemic administration led to reduction of developed obesity complication and improvement of body weight. If we take into consideration all studied parameters (body weight gain, weight gain rate, BMI, Lee index and related visceral fat weight), we make decision about more profitable use melatonin administration 1 h before lights-off then 1 h after lights-on. Moreover, the changes of these parameters did not connect with lower food consumption. These changes may be provide by stabilizing balance of anti-and proinflammation reaction, normalising circadian rhythm of adipokins secretion, appearing beige adipocytes, stimulating brown adipocyte differentiation, etc.

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ЕФЕКТ РІЗНИХ РЕЖИМІВ УВЕДЕННЯ МЕЛАТОНІНУ НА РОЗВИТОК ОЖИРІННЯ У ЩУРІВ, ІНДУКОВАНОГО ВИСОКОКАЛЮРІЙНОЮ ДІЄТОЮ

Останнім роками великі увага приділяється вивченню можливостей використання мелатоніну для покращення стану, виклика-
ного ускладненнями при ожирінні. Мета нашого дослідження полягало у визначенні впливу різного часу введення мелатоніну на зміну ваги тіла у щурів з ожирінням, викликаєм висококалорійною дієтою. Застосування мелатоніну в дозі 30 мг/н на протяженні 7 тижнів призводило до зниження маси вісцерального жиру, індексу Ті (як після ранкового, так і вечірнього введення) та швидкості приросту 
тіла (тільки після вечірньої дози).

Ключові слова: мелатонін, ожиріння, висококалорійна дієта, хронобіологія.

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ТЕМПЕРАТУРА РЕПРЕЗЕНТАТИВНИХ ЗОН ГРУДНОГО ВІДДІЛУ ВЕГЕТАТИВНОЇ НЕРВОВОЇ СИСТЕМИ, ЯК ПОКАЗНИК ФУНКЦІОНАЛЬНОГО СТАНУ ОРГАНІЗМУ ЛЮДИНИ

Дослідження температурної варіації репрезентативних зон грудного відділу вегетативної нервої системи шири 
людини після паренхімного інфаркту. Дослідження проводилось за допомогою змірювання температури інфрачерев
воним термометром нового покоління Medisana FTO D-53340. У дослідження брали участь 40 осіб, 20 з яких мали Q-інфаркт міокарда лівої шлуночки, а інші – ні.

Показано навіяння різниці температурних коефіцієнтів у репрезентативних зонах (р<0,05). Для лівої сторони хребта припам'ятована різниця у зементах Th1-Th5, що підтверджує діагноз: Th1 – 0,93±1,12 (контроль) та 
-0,79±2,49 (дослід). Th2 – 1,57±1,12 та -0,46±1,70, Th3 – 1,58±1,12, Th23 0,66±0,36, Th4 – 0,85±1,12, Th5 – 0,92±1,12 та -1,05±1,74

Для правої сторони Th6 – 0,85±0,73 (контроль) та -0,79±1,49 (дослід), Th7 – -1,00±0,79 та -1,37±0,69, Th8 – 
-0,96±0,73 та -0,99±1,68, Th9 – 0,12±0,64 та 0,38±1,13, Th10 – -0,12±0,14 та 1,03±1,00, Th11 – -1,69±1,05 та -1,86±0,16, Th12 – 
-1,65±1,15 та -1,96±1,12 відповідно.

Ключові слова: вегетативна нервова система, репрезентативні зони, температура, інфаркт.

Вступ. Нині розглядаються різні методи досліджен

нової температурних полей, теплобачення, радіотермометрія та ін. Хоч

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дують інші клінічні прояви, що дуже важливо для ран

ної діагностики та своєчасного лікування [2, 3].

На відміну від багатьох застосованих у сучасній медицині методів обстеження, інфрачеревна темпометрія та теплобачення задовольняють критерій діагностичних

них методів, які можуть застосовуватися для профілактичного обстеження [4].

Жоден з існуючих сьогоденних діагностичних методів не має такої широти діагностичного діапазону. Існує можли

вість застосувати теплобіометричний метод для обстеження будь-яких контингентів населення для цілей експрес-діагностики великої кількості захворювань [5].

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ISSN 1728-2624 ~ 27 ~

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Надійшла до редколегії 03.10.17.

УДК: 612.8

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