



# Melatonin as an effective pharmacocorrector of alimentary obesity resulting from a long-term excessive intake of palm oil

Elena Y. Bibik<sup>1</sup>, Natalia V. Shipilova<sup>1</sup>, Andrey V. Demenko<sup>1</sup>

<sup>1</sup> Lugansk State Medical University named after St. Luke, 1g 50-letiya Oborony Luganska Quarter, 91045, Ukraine

Corresponding author: Andrey V. Demenko ([pathecolgy@mail.ru](mailto:pathecolgy@mail.ru))

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## Abstract

**Introduction:** In the modern world, the problem of alimentary obesity is becoming one of the global problems affecting all countries. Desynchronization of bodily rhythms is another possible cause of development of alimentary obesity and metabolic syndrome. Thus, the purpose of this research was to study the influence of melatonin on the dynamics of body weight in rats.

**Materials and Methods:** The experiment was carried out on 150 white non-pedigree rats (females and males), which were divided into 3 groups (intact, control, experimental) and 3 series (immature, mature and senile rats). The animals of the control group received refined palm oil at a dose of 30 g/kg for a period of 6 weeks in their daily diet. The rats of the experimental group received melatonin at a dose of 1.9 mg/kg per day intragastrically for 35 days, after the 6-week period of excess palm oil intake was over. During the experiment, once every 7 days, the animals' weight check was done, followed by assessing the dynamics of weight gain in rats in different age groups.

**Results and Discussion:** It was determined that, in the group of the immature animals, an intake of palm oil resulted in the most obvious significant changes in the body weight over time. An increase in the total cholesterol and triglycerides concentration was observed in the biochemical blood tests of the animals of various age groups.

**Conclusion:** The use of melatonin at a dose of 1.9 mg/kg per day for 35 days proved highly effective in the animals of all age groups and led to a significant alignment of changes in the biochemical parameters studied in the rats of all ontogenesis periods.

## Keywords

alimentary obesity, palm oil, melatonin

## Introduction

At present, obesity is one of the most common chronic diseases in the world. Being an important biomedical problem, obesity makes a greater contribution to morbidity than infectious diseases (Perederiy et al. 2013, Burkov

and Ivleva Aya 2010, Solovyov et al. 2011). Overall, this problem is becoming one of those globally affecting all countries. According to the WHO data, there are over 1.7 billion people in the world who are overweight or obese. In most European countries, between 15% and 25% of the adult population suffer from obesity (Anonymous

2010, Bacquer et al. 2009). This pathology is most widespread in the United States, where the proportion of people suffering from obesity is 35% of the total population. It should also be emphasised that, according to the WHO data, in most countries of Europe from 25% to 70% of the population are overweight. In Russia, more than 60% of the population are overweight and about 26% suffer from obesity. The consequence is a 9-year decrease in life expectancy for women and a 12-year decrease for men (Vitebskaya 2010, Rapoport et al. 2013).

Moreover, the obesity rate in children and teenagers is observed to have been increasing worldwide of late: in well-developed countries, 25% of teenagers are overweight and 15% suffer from obesity. Being overweight in childhood is an important predictor of obesity in adulthood: 50% of children who were overweight at age 6 become obese in adulthood and, in adolescence, this probability increases to 80% (Averyanov 2009, Zagoruiko et al. 2010, Kartelishev and Smirnova 2013).

If the current trends continue, by 2030, the expected number of overweight people will have reached 3.3 billion people (Kravchuk and Galagudza 2014, Nduhiradandi et al. 2012).

In terms of gender, statistics are as follows: 10% of adult men and 14% of adult women in the world suffer from obesity, the total number reaching over 500 million people (Samorodskaya et al. 2015, Peschke and Mulhauer 2010).

Obesity is heterogeneous from the genetic, physiological and psychological points of view. It is considered to be a psychosomatic disease (Luzina et al. 2013). Depression and anxiety often precede the development of obesity and the degree of severity of mental symptoms correlates with anthropometric and biochemical disorders attributable to obesity (Romantsova 2011).

Over the last two centuries, widespread mechanisation and automation in everyday life and at work have resulted in hypodynamia in a significant portion of the population. An unhealthy lifestyle along with excessive consumption of food which is rich in fats and carbohydrates results in an imbalance in energy expenditure, certain changes in a number of biochemical processes and an increase in body weight (Strueva et al. 2013).

It has been recently found that another reason for the development of alimentary obesity and metabolic syndrome is desynchronisation of biological rhythms, which shows in disorders of internal organs due to the imbalance of the suprachiasmatic nucleus of the hypothalamus and depression of the secretory activity of the epiphysis (Arushanyan 2012a, Baksheev and Kolomoets 2011, Ryazanova 2014, Kitagawa et al. 2012). In the modern world, a person very often stays indoors with artificial lighting during night hours. These include: numerous nightspots, general illumination of buildings, streets, as well as the habit of staying in front of TV sets and various gadgets for an extended period.

The dysregulation of the sleep-wake cycle can be an etiological cause of insulin resistance and concomitant

systemic hyperinsulinemia (Ryazanova 2014, Dzherieva et al. 2012, Kotova 2011, Mikhailova and Shalenkova 2014).

A Belgian study by D. De Bacquer et al., 2012 demonstrated deterioration of the lipid profile accompanied by a decrease in the level of high-density lipoprotein (HDL) and an increase in the level of triglycerides (TG), as well as an increase in blood pressure (BP) and body weight, for people working in night-shifts compared to those working only during the daytime (Tereshchuk et al. 2014, Srinivasa et al. 2013). American scientists have determined the relationship between the time that the subject spends in front of the illuminated TV and computer screen and the development of abdominal obesity, dyslipidemia and hypertension (Sisson et al. 2009). Thus, it can be said that a prolonged period under constant artificial illumination, which is so typical of modern man, disrupts the physiological rhythm of work of the epiphysis and, possibly, acts as an additional factor that, together with overeating and low physical activity, leads to arterial hypertension, dyslipidemia and diabetes, all this resulting in sudden cardiovascular complications (Arushanyan 2012b, Arushanyan 2013a).

In this regard, of special interest for scientists now is melatonin, an epitope hormone, in whose spectrum of pharmacological activity there is an ability to improve microcirculation of blood in the brain, to activate cellular and humoral immunity, to increase stress resistance and to reduce chemotherapy toxicity. Melatonin involvement in the development of food aberrations has been proven, especially in a "night eating syndrome". An invert correlation has also been revealed between a urinary melatonin excretion level and a body mass index (Solovyov et al. 2011, Leroith 2012). Melatonin is synthesised mainly by the epiphysis (endocrine melatonin). Its concentration in blood of a healthy person throughout a day ranges from  $10^{-7}$ - $10^{-9}$  mg/ml (Arushanyan 2013b, Bibik and Shipilova 2015, Molchanov et al. 2011). Melatonin has immunomodulating, geroprotective, anticarcinogenic, biorhythmological, sedative, antidepressant and a general stimulating effect on the body (Molchanov et al. 2011, Arushanyan 2011a). In smaller amounts, melatonin is formed in diffuse neuroendocrine system cells, EC-cells of the gastrointestinal tract and immune cells (paracrine melatonin) (Rapoport et al. 2009, Grinenko et al. 2012).

Melatonin stimulates the transportation of glucose to the skeletal muscles via the IRS1/PI3K signalling pathway. The same signalling pathway leads to an increase in insulin secretion by  $\beta$ -cells (Molchanov 2012, She et al. 2009). When taking exogenous melatonin at a dose of 5 mg/day, patients demonstrate a decrease in body weight, partial normalisation of concentration of glucose, cholesterol, triglycerides and leptin in blood (Palios et al. 2012). The influence of melatonin on the regulation of adipose tissue is assumed to be made due to  $MT_1$  receptors, which enhance metabolic processes, but it has not yet been determined whether melatonin works directly or indirectly (Ryazanova 2014, Arushanyan 2011b).

At present, the proportion of palm oil in the diet of people living on the planet is substantially increasing. Its

use is determined first of all by its low cost and long shelf life. The trend towards an increase in demand for palm oil leads to the fact that the latter is becoming the basis for many kinds of mass consumption food (margarine, milk fat substitute, for manufacturing “cow milk”, “cream butter”, cottage cheese, yogurts, ice cream and processed cheese) (Amelyushkina et al. 2013, Ilyina and Radyuk 2012, Ipatova et al. 2009). Uncontrolled consumption of products containing palm oil should be considered as an etiologic factor of alimentary obesity (Yankovskaya et al. 2016, Cui et al. 2011).

In addition to the facts mentioned above, pharmacological therapy aimed at combating obesity has reached its critical stage, which is caused by the limited use of pharmaceutical products for weight loss due to their inefficiency and the risk of multiple dangerous side effects (Mirzoev 2015, Savelyeva 2011, Tereshchuk et al. 2014).

In this regard, studies aimed at finding effective and safe means of pharmacocorrection of alimentary obesity, caused by excessive consumption of palm oil are becoming more and more relevant.

In the light of the above, **the objective of this study** was to study the influence of melatonin on the dynamics of body weight changes in rats, which had consumed excessive amounts of palm oil for 6 weeks.

## Materials and Methods

The experiment was carried out on 150 white non-pedigree rats (females and males), which were divided into 3 groups and 3 series (immature, mature and senile rats): 50 immature rats weighing 50–70 g; 50 mature rats weighing 180–240 g and 50 senile rats weighing 260–300 g. The first group is intact. The animals of the second group (control group) received refined palm oil at a dose of 30 g/kg on a daily basis for a period of 6 weeks. The rats of the third group (experimental group) received melatonin intragastrically at a dose of 1.9 mg/kg per day for 35 days, after a 6-week period of excessive palm oil intake. During the experiment, once every 7 days, the animals' weight check was done, followed by assessing the dynamics of weight gain in rats in different age groups.

Over that period of time, such criteria as body weight gain, animals' behaviour, their appetite and external signs were evaluated. The qualitative criterion of obesity development in animals was body weight gain when consuming palm oil as a part of their daily diet. When identifying glucose, total cholesterol and triglycerides, a colorimetric enzymatic method was used, with esterase, cholesterol and glucose oxidase on an analyser Accent-300. The obtained results were processed statistically on an Intel Core 2 Duo 3.0 GHz personal computer using standard applied software packages – Microsoft Windows XP Professional, Microsoft Office 2003, Microsoft Excel Stadia 6.1/prof and Statistica.

The rats were decapitated after a 5-week pharmacocorrection with melatonin. The experimental animals

were kept in the vivarium of State Institution of Lugansk People's Republic “Lugansk State Medical University named after St. Luke” (with a natural light regime, at a temperature of 22–24 °C, relative air humidity 40–50%). The studies were carried out in accordance with the rules of good laboratory practice in preclinical studies in the Russian Federation (Order of the Ministry of Healthcare and Social Development of the Russian Federation of 23 August 2010, No. 708H), as well as with the rules and International Recommendations of the European Convention for the Protection of Vertebrate Animals Used for Experimental and other Scientific Purposes (1997).

## Results and Discussion

The long-term intake of palm oil by the rats in the control group resulted in a dramatic increase in their body weight in dynamics compared to the indicators in the rats of the intact group of all the ontogenetic periods under study (Table 1). Significantly important statistical differences in the rats' weights of the intact and control groups were established by the authors during the end period of observation. Thus, by the end of the third week of an excessive intake of palm oil, the body weight of immature rats exceeded that of the animals of the intact group by 48.5% and by the end of the sixth week it was twice as great.

Mature animals that received palm oil added to their daily diet gained 26.1% of weight for females and 20.1% for males by the end of the third week. The excess body weight of mature rats by the end of the sixth week reached 44.9% for females and 35.1% for males. The study of the data on body weight gain of senile rats of both sexes showed an unreliable difference in the first three weeks of the experiment, but by the end of the sixth week, a weight gain of 34.1% for females and 40.4% for males was recorded.

Continuous intake of palm oil by the rats of the second group showed a tendency to a dramatic increase in body weight in dynamics, in comparison with the indices of the rats of the intact group for all the periods of ontogenesis under study (Figs. 1–5).

Thus, by the end of the third week of consuming excessive amounts of palm oil, the body weight of immature rats exceeded that of the animals of the intact group by 48.5% and, by the end of the sixth week, it was twice as great.

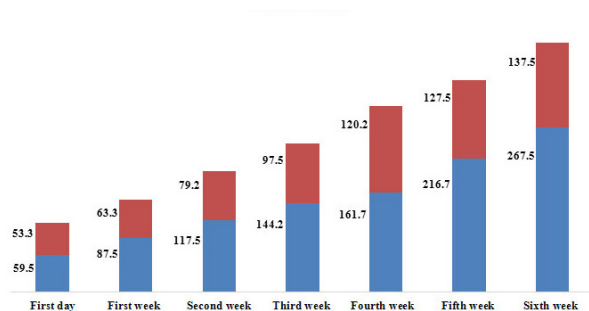
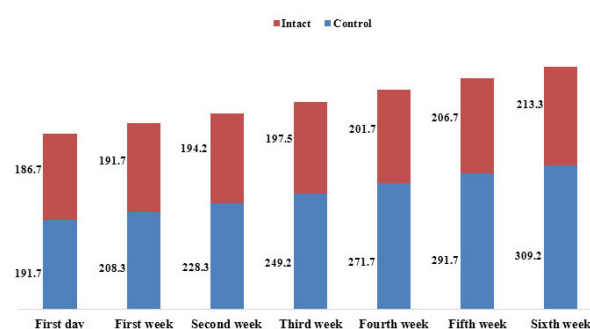
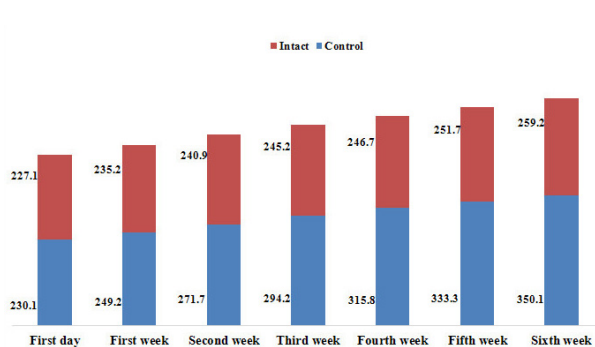
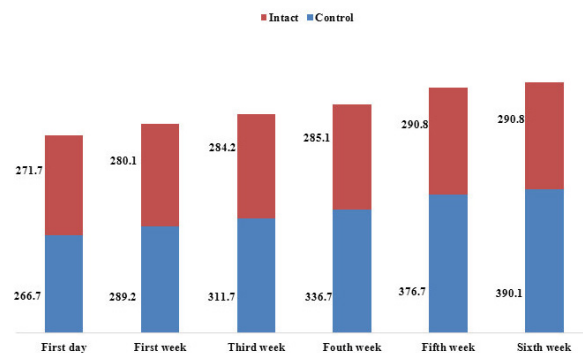
An analysis of the body weight gain rate of immature rats showed a linear trend dependence over the period of observing the animals. For the animals of the control group, this dependence had the form:  $f(x) = 14.28 \cdot (N-1) + Mo$ , (1) where N is a day of observation (from 1 to 7) and Mo is the initial mass at the beginning of the observation.

For the animals that received an excessive amount of palm oil in their diet, the only difference in the dependence was the value of the coefficient and this dependence can be represented as:  $f(x) = 35 \cdot (N-1) + Mo$ , (2), where N and Mo are the same as in formula (1) above.

**Table 1.** Dynamics of Body Weight Gain in Male and Female Rats of Various Age Groups, Consuming Palm Oil in Excess (M ± m, n = 6-12).

Group	Experiment time (weeks)					
	1	2	3	4	5	6
Immature rats intact group	63.33 ±2.10	79.16 ±2.71	97.50 ±1.70	141.16 ±2.00	127.50 ±2.50	137.01 ±1.70
Immature rats control group (palm oil)	87.50 ±2.14	117.50 ±2.14	144.16± 3.51*	161.66 ±4.40	216.66 ±3.07*	267.50 ±3.59*
Mature females, intact group	191.66 ±3.33	194.16 ±2.38	197.50± 3.09	201.66 ±3.07	206.66 ±2.47	213.33 ±1.66
Mature females, control group	208.33 ±5.86	228.33 ±6.66	249.16± 5.83*	271.66 ±66.6*	291.68 ±4.94*	309.16 ±3.27*
Mature males, intact group	235.00 ±3.65	240.83 ±4.16	245.0 ±4.65	246.66 ±3.80	251.66 ±3.80	259.16 ±3.27
Mature males, control group	249.16 ±4.16	271.66 ±6.14	294.16 ±5.54	315.83 ±4.90*	333.33 ±5.42*	350.00 ±7.30*
Senile male rats, intact group	293.33 ±4.21	297.50 ±3.81	303.33 ±3.33	310.00 ±3.16	314.00 ±3.00	321.66 ±2.78
Senile male rats, control group	311.66 ±6.41	335.83 ±8.20	361.66 ±8.53*	387.50 ±6.80*	409.16 ±6.63*	451.66 ±7.03*
Senile female rats, intact group	280.00 ±3.41	284.16 ±3.96	285.00 ±3.87	289.16 ±4.16	290.83 ±4.36	292.50 ±3.59
Senile female rats, control group	289.16 ±8.36	311.66 ±9.71	336.66 ±6.14	365.00 ±5.62*	376.66 ±6.66*	390.00 ±8.56*

Note: \* - P (<0.001) compared to intact group

**Figure 1.** Dynamics of body weight gain in immature rats, consuming palm oil.**Figure 2.** Dynamics of body weight gain in mature female rats, consuming palm oil.**Figure 3.** Dynamics of body weight gain in mature male rats, consuming palm oil.**Figure 4.** Dynamics of body weight gain in senile female rats, consuming palm oil.



Both functions are of relative nature and can be specified by dividing the observation period into separate segments, but they fully reflect the tendencies of body weight gain. No significant differences between the experimental data and the data described in the above formulae are observed (1, 2).

Mature animals that consumed palm oil added to their daily diet had an increase in weight by the end of the third week – 26.1% for females and 20.1% for males. Excess body weight of mature rats by the end of the sixth week was 44.9% for females and 35.1% for males.

The study of the data on the body weight gain of senile rats of both sexes showed an unreliable difference in the first three weeks of the experiment, but by the end of the sixth week, a weight gain of 34.1% for females and 40.4% for males was recorded.

As can be seen from the above, the data obtained in the series of experiments prove that excessive consumption of palm oil at a dose of 30 g/kg for 6 weeks leads to the second- and third-degree alimentary obesity in animals of all periods of ontogeny under study. The maximum increase in body weight (2 times) was observed in the group of immature animals. The pathological process that occurs under the above conditions can serve as an experimental model for alimentary obesity in white rats.

The results of the studies performed in terms of pharmacocorrection of alimentary obesity by means of melatonin have shown that the immature animals showed a gradual uniform loss of body weight for 5 weeks (Fig. 6). Conspicuous is the fact that the discontinuation of palm oil consumption in the control animals group does not result in body weight loss.

Mature animals that received melatonin as a pharmacocorrector also gradually lost weight and, by the end of the 5<sup>th</sup> week, their weight was at the level of the rats from the intact group (Fig. 7).

In the experimental group of senile rats of both sexes, a decrease was found in body weight in comparison with that in the animals of the control group (Fig. 8) which, by the end of the experiment, was comparable to the indices in the intact group.

Continuous consumption of palm oil by the rats of the control group indicated a tendency for a dramatically increased concentration of glucose in blood, compared to the indices of the rats from the intact group for all the periods of ontogenesis under study (Table 2). Thus, by the end of the experiment, the level of glucose in the blood of immature rats exceeded that of the animals in the intact group by 55.53%. In the group of mature animals, this difference was 61.62% and for senile rats – 41.01%.

Comparing the values of total cholesterol in the biochemical analysis of blood of the immature animals from the control group with the similar indices of the intact group rats under the conditions of this experiment, an increase of 1.82 times was found. For mature animals consuming palm oil in excess, total cholesterol values also increase 1.72 times and for senile rats – 1.61 times.

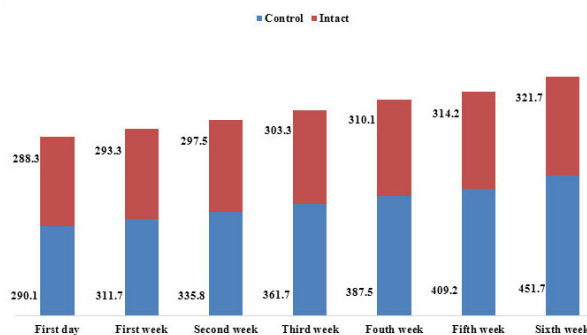


Figure 5. Dynamics of body weight gain in senile male rats, consuming palm oil.

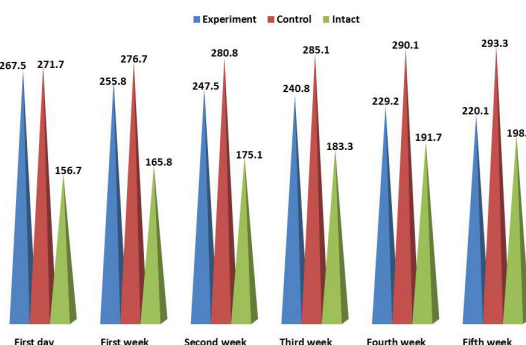


Figure 6. Dynamics of body weight gain in immature rats, in connection with pharmacocorrection by melatonin.

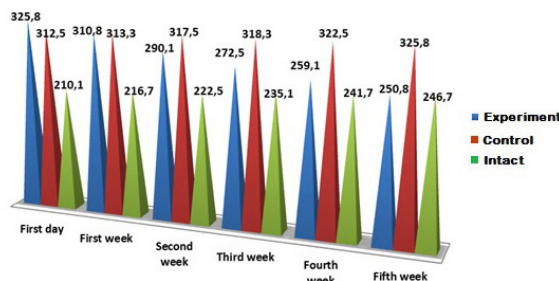


Figure 7. Dynamics of body weight gain in mature rats, in connection with pharmacocorrection by melatonin.

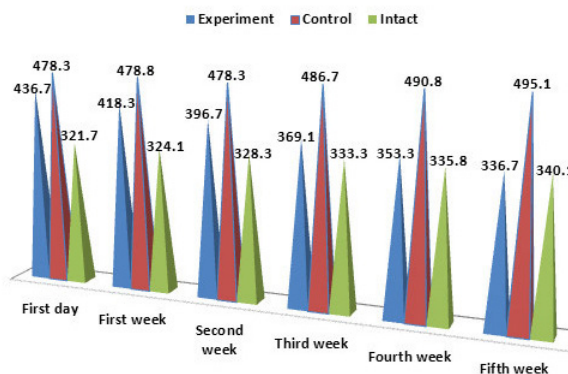


Figure 8. Dynamics of body weight gain in senile male rats, in connection with pharmacocorrection by melatonin/8.

**Table 2.** Dynamics of Changes in Rats' Biochemical Parameters after Excessive Consumption of Palm Oil and Pharmacocorrection by Melatonin (M±m, n=6-12).

Animal group		Glucose, mmol/L	Total cholesterol, mmol/L	Triglycerides, mmol/L
Intact	Immature	4.43±0.15	1.47±0.10	0.19±0.08
	Mature	4.56±0.16	1.61±0.05	0.18±0.15
	Senile rats	4.95±0.19	1.77±0.17	0.18±0.11
Control	Immature	6.89±0.20*	2.68±0.09*	0.67±0.34*
	Mature	7.37±0.24*	2.78±0.18*	0.76±0.45*
	Senile rats	6.98±0.22*	2.85±0.12*	0.77±0.40*
Experiment	Immature	4.97±0.27	1.97±0.06	0.29±0.02
	Mature	5.15±0.13	2.07±0.10	0.36±0.15
	Senile rats	5.56±0.21	2.12±0.08	0.38±0.21

Note: \* - P (<0.001) compared to control group.

As it can be seen from Table 2, the triglycerides concentration in blood of the immature animals of the control group is characterised by a dramatic (3.53 times) increase in comparison with the indices recorded in the intact animals. The mature rats which consumed an excessive amount of palm oil in this experimental study had a triglyceride level exceeding the normal values by a factor of 4.22. Similar differences were found in the group of senile rats.

In the immature animals that received melatonin as a pharmacocorrector for 5 weeks, the level of glucose in blood slightly exceeds the values recorded in the intact group rats. However, it is lower by 27.87% than the indices in the group of rats that were on a high-fat diet consuming palm oil. The mature animals that were given melatonin as a pharmacocorrector for alimentary obesity were characterised by a reduced blood glucose level, 30.13% lower than the indicators in the control group. The blood glucose concentration in the senile rats that received melatonin after a long consumption of palm oil decreased by 20.35% compared to those in the control group. However, over a 35-day period of pharmacocorrection, they did not reach the values of the intact group animals.

The values of total cholesterol in the blood of the immature rats of the experimental group were 73.51% of those recorded in the rats of the control group. The mature animals that received melatonin as a pharmacocorrector were also characterised by a reduced concentration of total cholesterol in their blood compared to those in the control group. In the experimental group of senile rats of both sexes, no fully stabilised level of total cholesterol in blood was detected, but rather a steady tendency to its decrease in comparison with the control values.

The concentration of triglycerides in the blood of the immature animals of the experimental group is characterised by stabilisation, although it does not reach the values recorded in the intact animals. In this experimental study, the mature rats that received an excessive amount of palm oil in their diet and melatonin as a pharmacocorrector had a triglyceride level that exceeded the normal

values by a factor of two. Similar changes were detected in the group of senile rats.

Introduction of 30 g/kg of palm oil into a diet for 6 weeks leads to a 1.6–1.8-times increase in the concentration of total cholesterol in the biochemical analysis of blood of animals of different age groups compared to similar indices for the intact group rats. The concentration of triglycerides in the blood of animals which received palm oil in excess is characterised by a dramatic (3.5 to 4.2 times) increase in comparison with the rates recorded in the intact animals. The use of melatonin at a dose of 1.9 mg/kg per day as a pharmacocorrector of alimentary obesity leads to a significant levelling of changes in the biochemical indices of rats of different periods of ontogenesis.

## Conclusions

The results of the studies performed in terms of pharmacocorrection of alimentary obesity by means of melatonin identified that the immature animals showed a gradual uniform loss of body weight for 5 weeks. Conspicuous is the fact that the discontinuation of palm oil consumption in the control animals group does not result in body weight loss.

Introduction of 30 g/kg of palm oil into a diet for 6 weeks leads to a 1.6–1.8-times increase in the concentration of total cholesterol in the biochemical analysis of blood of animals of different age groups compared to similar indices for the intact group rats. The concentration of triglycerides in the blood of animals which received palm oil in excess is characterised by a dramatic (3.5 to 4.2 times) increase in comparison with the rates recorded in the intact animals. The use of melatonin at a dose of 1.9 mg/kg a day as a pharmacocorrector of alimentary obesity leads to a significant levelling of changes in the biochemical indices of rats of different periods of ontogenesis.

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## Contributors

- **Elena Y. Bibik**, holder of Habilitation Degree in Medicine, Professor, Head of the Department of Fundamental and Clinical Pharmacology, e-mail: [helen\\_bibik@mail.ru](mailto:helen_bibik@mail.ru). Contribution of the author: 30%. Was responsible for relevance of the topic, choice of research methods and research for modern sources of literature.
- **Natalia V. Shipilova**, Teaching Assistant of the Department of Technology of Medicines, Organisation and Economics of Pharmacy, e-mail: [n.v.shipilova@mail.ru](mailto:n.v.shipilova@mail.ru). Contribution of the author: 50%. Conducted experimental studies, described the results and prepared a design of the article in accordance with the requirements.
- **Andrey V. Demenko**, PhD in Medicine, Assistant Professor of the Department of Fundamental and Clinical Pharmacology, e-mail: [pathecolgy@mail.ru](mailto:pathecolgy@mail.ru). Contribution of the author: 20%. Did the statistical processing of the obtained research results. *Bit et lab iliquam velendis necto blate ditas sequodioste voluptatius sunt.*