

## **Influence of natural and artificial lighting and melatonin administration on the exercise capacity in rats**

*Influența luminii naturale și artificiale și a administrării de melatonină asupra capacității de efort fizic la șobolani*

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### **Abstract**

*Background.* Lighting conditions influence daily professional and physical activities of humans. Melatonin secretion is dependent on environmental photoperiodicity and its rhythm changes may contribute to systemic dysfunctions.

*Aims.* The study evaluates the effect of natural and artificial lighting on exercise capacity and in the same conditions of natural and artificial lighting, the effect of melatonin supplementation on exercise capacity and cardiovascular changes.

*Methods.* The research was conducted on 4 groups of animals (n = 10 animals/group) exposed to natural or artificial lighting, supplemented or not with melatonin and subjected to physical exercise.

*Results.* Significant increases in aerobic exercise capacity (AEC) after training were observed in animals exposed to natural lighting, compared to those exposed to artificial lighting; there were significant decreases of AEC in animals supplemented with melatonin, exercise trained and subjected to natural and artificial lighting, compared to those obtained in animals without melatonin administration. The cardiovascular indicators, determined two weeks after exercise, showed impaired cardiovascular adaptation.

*Conclusions.* Both natural and artificial lighting increased aerobic exercise capacity, though the latter in a more reduced manner. Melatonin supplementation decreased aerobic exercise capacity under natural and artificial lighting conditions. Artificial lighting, with and without melatonin supplementation, affected cardiovascular adaptation to exercise.

**Key words:** natural lighting, artificial lighting, melatonin, exercise.

### **Rezumat**

*Premize.* Există dovezi care atestă că expunerea la lumină influențează activitățile profesionale și fizice zilnice ale omului. Secreția de melatonină este dependentă de fotoperiodicitatea din mediu și orice modificare de ritm secretor poate contribui la disfuncții sistemice.

*Obiective.* Studiul urmărește pe de o parte evaluarea efectului expunerii la lumină naturală și artificială asupra capacității de efort fizic și pe de altă parte în ce măsură suplimentarea cu melatonină, în aceleași condiții de iluminare, influențează capacitatea de efort fizic și activitatea cardiovasculară la șobolani.

*Metode.* Pentru efectuarea studiului s-au utilizat 4 loturi de animale (n=10) expuse la lumină naturală și artificială, supuse efortului fizic, la care s-a administrat sau nu melatonină.

*Rezultate.* Rezultatele obținute au arătat o creștere semnificativă a capacității de efort fizic aerob (AEC) la animalele expuse la lumină naturală comparativ cu cele expuse la lumină artificială; AEC a scăzut semnificativ la animalele supuse efortului fizic, expuse la lumină naturală și artificială, la care s-a administrat melatonină, comparativ cu valorile obținute la animalele fără administrare de melatonină. Parametrii cardiovasculari, apreciați la două săptămâni după efortul fizic, au arătat o alterare a adaptării cardiovasculare.

*Concluzii.* În concluzie, putem afirma că atât lumina naturală, cât și cea artificială au crescut capacitatea de efort fizic aerob, efectul luminii artificiale fiind mai redus. Suplimentarea cu melatonină a diminuat capacitatea de efort fizic aerob în condiții de iluminare naturală sau artificială. Lumina artificială, cu sau fără administrare de melatonină, a interferat cu adaptarea cardiovasculară la efort fizic.

**Cuvinte cheie:** lumină naturală, lumină artificială, melatonină, efort fizic.

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## Introduction

Lighting is one of the fundamental elements that ensure optimal conditions for life and human activity (Duffy & Czeisler, 2009).

Natural lighting is provided by non-ionizing light radiation, at a wavelength of 0.4-0.7 micrometers, for which the main source is the sun (48% of solar radiation) (Knight et al., 2005). Light is an important factor for biorhythm, especially circadian rhythm. Natural lighting influences daily professional and physical activities conducted in the natural environment (Brown, 1994). Artificial lighting is used to ensure adequate brightness for daytime activities, nocturnal professional activities (shift work) and sports activities or nocturnal field competitions (\*\*\*, 2009). Luminescent or fluorescent artificial lighting, also named "cold light", is the closest to natural light, preferentially used and the most profitable in economic terms (\*\*\*, 2009).

However, light exposure is the best known acute suppressor of nocturnal melatonin; the invisible non-ionizing radiation in the extremely low frequency range (e.g., 60 Hz) seems to be able to modify pineal melatonin synthesis (Reiter & Richardson, 1992). In a research conducted under to different lighting conditions, a decrease in exercise capacity, changes in strategies for energy production and antioxidant protection were observed in aging animals (Vingradova et al., 2007).

Human physical activity can be considered as complex "stress" in terms of intensity and duration, during which the disruption of homeostasis causes favorable or unfavorable adaptive processes, with impact on exercise capacity. Exercise is beneficial to health, but during endurance or high intensity exercise and overtraining, the body generates reactive oxygen species which are known to result in oxidative stress; oxidative and nitrosative stress is caused by the imbalance between reactive oxygen and nitrogen species, with the inefficiency of antioxidant defense mechanisms. Exhausting physical exercise induces pro-oxidant effects (Dejica, 2001; Tache, 2001) and multiple neuromuscular, endocrine, metabolic, cardiopulmonary and psycho-emotional stress, associated with subsequent complications: inflammation and skeletal muscle lesions (Van Reeth, 1994), myocardial injury, kidney and liver failure, pulmonary edema (Vornicescu et al., 2013).

The administration of antioxidants, natural nutritional or synthetic non-nutritional ones, improves the body's antioxidant defense (Augustyniak et al., 2010; Powers et al., 2004; Yavari et al., 2015; Carochi & Ferreira, 2013; Surai, 2015; Martoma, 2009; Shebis et al., 2013). In line with this idea, melatonin (5-methoxy-N-acetyltryptamine, the major hormone produced by the pineal gland) is now widely used, being a very potent, endogenously produced free radical scavenger (with higher effects than those of vitamin E) (Pieri et al., 1995), a broad-spectrum antioxidant and an inexpensive drug with low toxicity and simple exogenous administration (Vornicescu et al., 2013; Ianăș et al., 1991). Melatonin is also a chronobiotic and chronohypnotic internal sleep facilitator (Vornicescu et al., 2013; Langer et al., 1997; Mistraletti et al., 2015; Morandi et al., 2015), its secretion being dependent on

environmental photoperiodicity or circadian light rhythm: daylight reduces its production, while the darkness of night increases it about 10 times (Reiter, 1997; Youngstedt et al., 2016). Most studies have shown a favorable effect of melatonin supplementation on exercise in animals (Vingradova et al., 2007; Hara et al., 1997; Bicer et al., 2012) and humans (Ochoa et al., 2011; Maldonado et al., 2012; Atkinson et al., 2001; Atkinson et al., 2005).

Importantly, recent research suggests that melatonin plays an influent and general beneficial role in various cardiovascular diseases, including heart failure and myocardial injury, hypertension and atherosclerosis (Pandi-Perumal et al., 2016; Dominguez-Rodriguez, 2012; Sun et al., 2016). Decreased melatonin levels were reported in all cardiovascular pathological conditions (Pandi-Perumal et al., 2016). Melatonin may affect cardiovascular pathophysiology via both receptor-mediated and receptor-independent mechanisms (Dominguez-Rodriguez, 2012). Two classic melatonin membrane receptors (MT1 and MT2), known to be present in the heart and vascular system, have dual effects, vasoconstriction and vasodilatation, and can generate both beneficial and unfavorable effects (Dominguez-Rodriguez, 2012); however, the receptor-independent actions of melatonin relate to its protective antioxidant function (Dominguez-Rodriguez, 2012). Considering that cardiovascular diseases are the first cause of death worldwide, the low toxicity and possible cardioprotective role of melatonin could have important clinical implications.

## Objectives

This experimental study was designed to evaluate the effect of natural and artificial lighting on exercise capacity and in the same conditions of natural and artificial lighting, the effect of melatonin supplementation on exercise capacity and cardiovascular changes.

## Hypothesis

Melatonin supplementation during light exposure, both in artificial and natural conditions, can modulate the exercise capacity and cardiovascular parameters of rats by its antioxidant effect. The effects depend on the melatonin dose, type of exercise, age of animals and duration of light exposure.

## Material and methods

The research was approved by the Ethics Board of the "Iuliu Hațieganu" University of Medicine and Pharmacy Cluj-Napoca.

### *Research protocol*

#### *a) Period and place of the research*

The research was conducted in the Experimental Research Laboratory of the Department of Physiology of the "Iuliu Hațieganu" University of Medicine and Pharmacy Cluj-Napoca, between January 2014 - April 2014.

#### *b) Subjects and groups*

The study was performed on Wistar rats aged 18 weeks, weighing 180-200 g, maintained in adequate vivarium conditions: temperature and humidity, normocaloric food

20 g/day/animal, granulated fodder, water *ad libitum*.

#### Groups

The research was conducted on 4 groups of animals (n = 10 animals/group):

- group I - supplemented with melatonin, exposed to natural lighting, and subjected to physical exercise;
- group II - supplemented with melatonin, exposed to artificial lighting, and subjected to physical exercise;
- group III - exposed to natural lighting and subjected to physical exercise;
- group IV - exposed to artificial lighting and subjected to physical exercise.

#### c) Tests applied

The testing of aerobic exercise capacity (AEC) was based on the swimming test in a pool 100/40/60 cm in size, with a water level of 30 cm and a water temperature of 21-23°C (Nayanatara et al., 2005). The measurements were carried out at 07.00 am. AEC was measured in seconds. The duration of exercise was 14 days. The studied time points were day 1, day 7, and day 14.

Cardiovascular changes during exercise based on direct measurements of blood pressure (BP) and heart rate variability and indirect measurements of pulse pressure and mean arterial pressures were assessed by using a blood pressure device (sleeve tail) and a Biopac MP 150 device. BP values were expressed in mm Hg, and heart rates were expressed in cycles/min. The measurements were made on day 14, one hour after the end of the experiment.

The animals were exposed to moderate 40 W artificial fluorescent lighting at an intensity <50 Lux, at 1.5 m distance from the animal, for 24 hours, daily, during 14 days.

Melatonin, Mellow Tonin (Secom®), was administered in a dose of 3 mg/kg body weight, by oropharyngeal gavage, at 06.00 am, before exercise, for 14 days.

#### d) Statistical processing

Descriptive statistics elements were calculated, and data were presented using indicators of centrality, location and distribution.

To test normal distribution, the Shapiro-Wilk test was used. If data had a normal distribution, the ANOVA or t (Student) test was used; in the case of an uneven distribution of values or ranks, the non-parametric Kruskal-Wallis, Mann-Whitney (U) or Wilcoxon test was employed. The level of statistical significance for the tests used was  $\alpha = 0.05$  (5%).

Statistical processing was performed with Excel (Microsoft Office 2007) and with the Stats Direct v.2.7.2 program. The results were graphically represented using Excel (Microsoft Office 2007).

## Results

a) The influence of melatonin supplementation on AEC under natural and artificial lighting conditions was studied in groups I and II; the influence of natural and artificial lighting on AEC was studied in groups III and IV (Figure 1 and Tables I, II).

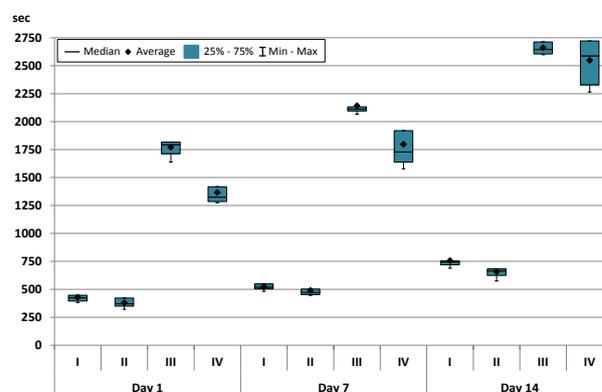


Fig. 1 – Exercise capacity values (seconds) in the studied groups.

Table II

Comparative analysis and statistical significance for exercise capacity values (seconds) in the studied groups - effects of time variance.

Group \ Time	Time variance (p)		
	D1-D7	D7-D14	D1-D14
G I	< 0.001	< 0.01	< 0.01
G II	< 0.01	< 0.01	< 0.001
G III	< 0.01	< 0.01	< 0.001
G IV	< 0.01	< 0.01	< 0.01

Our results show the following:

- AEC significantly increases in trained animals exposed to natural and artificial lighting after 14 days, compared to initial values;
- AEC significantly increases after 7 days of training in animals exposed to natural lighting, compared to those exposed to artificial lighting;
- AEC significantly decreases in animals supplemented with melatonin, exercise trained and subjected to natural and artificial lighting, compared to non-supplemented animals;
- AEC significantly increases after 14 days in animals supplemented with melatonin, exercise trained and subjected to natural and artificial lighting, compared to initial values.

Considering all four groups together, at each evaluation moment (day 1, 7 and 14), highly statistically significant variances were recorded ( $p < 0.001$ ).

Table I

Comparative analysis and statistical significance for exercise capacity values (seconds) in the studied groups - effects of testing conditions.

Parameter	Melatonin effect		Lighting effect		Combined effect	
	I-III groups (Natural)	II-IV (Artificial)	I-II (Mel+Ex)	III-IV (Ex)	I-IV (Mel+N/A)	II-III (Mel+A/N)
Day \ p	p	p	p	p	p	p
D1	< 0.001	< 0.001	< 0.05	< 0.001	< 0.001	< 0.001
D7	< 0.001	< 0.001	NS	< 0.01	< 0.001	< 0.001
D14	< 0.001	< 0.001	< 0.01	NS	< 0.001	< 0.001

Legend: Mel - melatonin, Ex - exercise, N - natural lighting, A - artificial lighting, NS - non-significant.

**Table III**

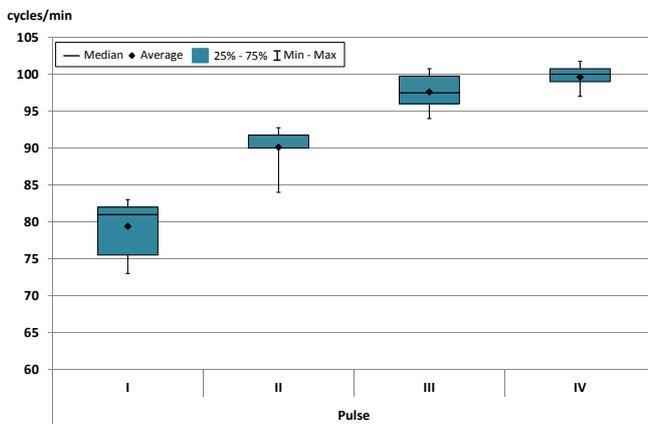
Comparative analysis and statistical significance for pulse rates (cycles/min), systolic and diastolic BP, mean BP (mm Hg) and pulse pressure in the studied groups - effects of testing conditions.

Parameter groups	Melatonin effect		Lighting effect		Combined effect	
	I-III (Natural)	II-IV (Artificial)	I-II (Mel+Ex)	III-IV (Ex)	I-IV (Mel+N/A)	II-III (Mel+A/N)
Cardiovascular parameter \ p	p	p	p	p	p	p
Pulse	< 0.001	< 0.001	< 0.001	< 0.05	< 0.001	< 0.001
Systolic BP	< 0.001	< 0.001	< 0.01	< 0.001	< 0.001	< 0.001
Diastolic BP	< 0.05	< 0.001	NS	< 0.001	< 0.001	< 0.01
Average BP	< 0.001	< 0.001	NS	< 0.001	< 0.001	< 0.001
Pulse pressure	< 0.01	< 0.001	< 0.05	< 0.001	< 0.001	< 0.001

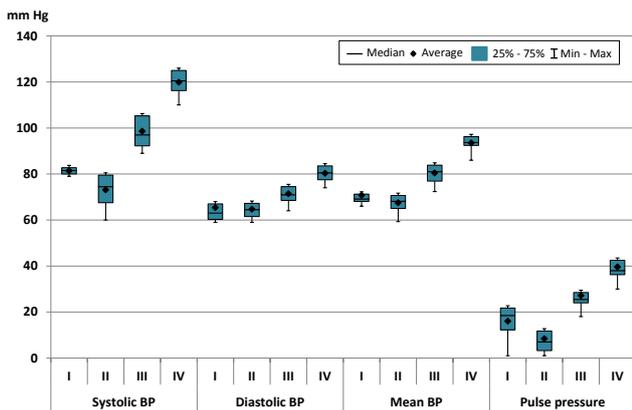
Legend: Mel - melatonin, Ex - exercise, N - natural lighting, A - artificial lighting, NS - non-significant.

Considering all three evaluation moments together, in each group (group I, II, III and IV), highly statistically significant variances were recorded ( $p < 0.001$ ).

b) Cardiovascular changes under the influence of melatonin supplementation and lighting, depending on exercise (Figures 2, 3 and Table III).



**Fig. 2** – Pulse rates (cycles/min) in the studied groups.



**Fig. 3** – Systolic and diastolic BP, mean BP (mm Hg) and pulse pressure in the studied groups.

The cardiovascular indicators determined one hour after exercise show impaired cardiovascular adaptation:

- significant increases in heart rate and significant decreases in systolic BP and pulse pressure in exercise trained animals exposed to artificial lighting and

supplemented with melatonin (group II), compared to animals exposed to natural lighting and supplemented with melatonin (group I);

- significant increases in pulse, systolic BP, diastolic BP, mean BP and pulse pressure in exercise trained animals exposed to artificial lighting (group IV), compared to animals exposed to natural lighting (group III).

The comparative analysis in the studied groups also showed no statistical significance for diastolic BP and average BP between groups I and II (melatonin supplemented), a statistical significance ( $p < 0.05$ ) for pulse values between groups III and IV (natural and artificial lighting), for diastolic BP between groups I and III (natural lighting) and for pulse pressure between groups I and II (melatonin supplemented), and a highly statistical significance ( $p < 0.001$ ) between all other two groups.

Considering all four groups together, for all parameters measured: pulse rates (cycles/min), systolic and diastolic BP, mean BP (mm Hg) and pulse pressure, highly statistically significant variances were recorded ( $p < 0.001$ ).

## Discussions

Several studies mentioned a relationship between melatonin and light, melatonin and exercise, or the favorable or unfavorable effects of melatonin supplementation on our body, in correlation with oxidative stress (Pandi-Perumal et al., 2016; Dominguez-Rodriguez, 2012; Sun et al., 2016). However, in the literature, we found little evidence about the combined effect of melatonin supplementation and lighting conditions on exercise capacity and cardiovascular response.

Our results concerning the reaction of the body in relation to the above mentioned parameters were compared with the research of other authors, in animals and humans. The value of this experimental study resides in the complex statistical analysis that evaluates and compares all these multiple variables that influence each other.

As it was expected, in our research the best AEC results were obtained by the trained animals exposed to natural lighting. This may be due to neuroendocrine mechanisms activated by physical stress, mainly to the sympathoadrenal system and the hypothalamic-pituitary-adrenal axis (Staicu & Tache). Sun exposure or exercise in natural lighting improves hormonal responses (blood melatonin), quality of sleep and therefore, physical status and quality of life (Lee et al., 2014; Atkinson et al., 2008). There is an exercise-related increase of melatonin levels, which is

more pronounced in the morning (Marrin et al., 2011). AEC values were also increased in subjects trained under artificial lighting conditions. The results correlate well, given the fact that fluorescent light is similar to natural light (\*\*\*, 2009) and the same neuroendocrine mechanisms are involved. The minimal differences that occurred between these two parameters are possibly due to stress caused by artificial lighting, with an inhibitory effect on melatonin secretion (Reiter & Richardson, 1992; Golombek et al., 1992) and changes in the circadian rhythm (in rats, melatonin secretion from the pineal gland is circadian and closely coupled to circadian rhythms during physical exercise) (Tamarkin et al., 1980). In line with this idea, it was observed that in rats, swimming suppresses melatonin content of the pineal gland, by increasing the outflow of melatonin (Troiani et al., 1988). Moreover, it seems that melatonin suppression induces enhanced immobility in the forced swimming test model (through excessive release of serotonin) (Voiculescu et al., 2015), which can also explain the lower AEC values observed by us in trained animals subjected to artificial lighting.

Exercise can influence melatonin levels (Van Reeth, 1994). Non-photoc stimuli can exert phase shifts in human circadian rhythms (Van Reeth, 1994), but reports on the induction of phase advances in melatonin rhythm through exercise are rarer, as are the effects of phase-shift in body temperature rhythm (Atkinson et al., 2007). In another study in which participants were exposed to bright light (10,000 lux) or remained in dim light (<50 lux), it was observed that a light program based on chronobiological rhythm can reduce basal temperature during morning effort in hot conditions (Atkinson et al., 2008).

Studies regarding the effect of melatonin supplementation on animal activity and behavior have provided mixed results. It appears that the effect of melatonin supplementation on exercise capacity is dose and age-dependent.

Several papers have shown the beneficial effect of melatonin administration during physical exercise in animals. It is well known that exercise (e.g., swimming) imposes severe oxidative stress and increases lipid peroxidation in the liver, muscle and brain. Pre-treatment with melatonin, and other indoleamines to a lesser extent (5-methoxytryptamine, 5MT, or 6-hydroxymelatonin, 6HM), provided protection against oxidative damage associated with swimming for 60 minutes (Hara et al., 1997). Antioxidant supplementation can improve the lipid profile and exercise capacity of trained rats (Kim et al., 2004). In acute exercise, increased production of free radicals and inhibition of antioxidant activity are prevented by melatonin administration (Bicer et al., 2012). In the melatonin-treated groups, decreases in the plasma concentrations of IL and TNF- $\alpha$  were recorded (Borges Lda et al., 2015). In mature and senescent animals, melatonin had a stimulating effect on age-related physical activity, such as a reduction of exercise capacity depression and normalization of antioxidant protection (Vingradova et al., 2007). Even some exercise-induced disorders (liver, kidney and nervous system inflammatory damage) were ameliorated with melatonin treatment through antioxidant capacity and other beneficial endogenous effects (Gedikli

et al., 2015; Lee et al., 2015). In humans, oral melatonin supplementation associated with acute physical exercise reversed oxidative stress, improved defense and lipid metabolism, and led to an improvement in fitness capacity (Maldonado et al., 2012). Melatonin supplementation before intense physical exercise reduced muscle damage by modulating the associated oxidative stress and inflammatory signaling (Ochoa et al., 2011).

Other studies discussed the unfavorable effects of melatonin (Pandi-Perumal et al., 2016; Sun et al., 2016; Arushanian & Ovanesov, 1989; Arushanian et al., 1989). When administered in a low dose (0.1 mg/kg), pineal melatonin either induced no change or decreased the rats' locomotor activity and exploratory behavior (Arushanian & Ovanesov, 1989), but when administered in young animals (at 4 months of age), melatonin did not influence their exercise capacity (Vingradova et al., 2007). High doses (1.0 and 10.0 mg/kg) were effective only in the night hours (01.00-03.00); during the day, the effect of 1.0 mg/kg hormone administration generated increased immobility (Arushanian & Ovanesov, 1989). In rats, melatonin induced an imipramine-like effect on circadian mobility, and potentiated the antidepressant action in animals with a low baseline locomotor activity (Arushanian et al., 1989). Animal studies also suggested that melatonin had dual effects on the vasculature, depending on the specific type of activated receptor (MT1 or MT2) (Pandi-Perumal et al., 2016); MT1-activation generated vasoconstriction and MT2-activation induced vasorelaxation (Pandi-Perumal et al., 2016). It appears that these receptors are not related to the melatonin protective direct free radical scavenging properties and impaired protection of heart and brain.

In our research, AEC decreased in trained animals supplemented with melatonin, probably due to circadian rhythm disturbances in the groups subjected to natural and artificial lighting, to sleep disturbances and fatigue (Ponsford, et al., 2012); in addition, the inhibitory pro-oxidant effect of melatonin in high doses (3 mg/kg/day), with reduced antioxidant defense and decreased locomotor activity (as it was presented above) (Arushanian & Ovanesov, 1989) can be involved. It is not known whether there are significant residual effects of this hormone on physical performance in trained subjects (Arushanian et al., 1989). Further research is needed regarding the daytime effects of melatonin administration on performance. Nevertheless, AEC values increased over time (on day 14 compared to day 7), and this was interpreted as an adaptation of the body to exercise and lighting conditions with a beginning of melatonin's beneficial effect, which in time could exceed the high values of non-supplemented animals. Moreover, it is known that exposure of the body to metabolic, oxidative and inflammatory stress from chronic high-intensity training could lead to homeostatic balance which controls these responses and prepares the body for the training sessions, for the benefit of performance in athletes (Huertas, 2011). The duration of melatonin supplementation could also have been too short, in humans being proved that melatonin has a positive effect in modulation of the circadian cycle (and improving sleep), after four weeks of daily treatment (Leonardo-Mendonça et al., 2015).

It is well documented that intensity and duration of exercise influence a considerable number of physiological variables (Beck et al., 2015), e.g. blood pressure and heart catalase activity (Barbosa et al., 2013).

In our study, an impaired cardiovascular adaptation was observed in exercise trained animals supplemented with melatonin; significant increases in heart rate and significant decreases in systolic BP and pulse pressure were determined in subjects exposed to artificial lighting, in comparison with those exposed to natural lighting and exercise trained animals non-supplemented with melatonin; significant increases in all parameters (pulse, systolic BP, diastolic BP, mean BP and pulse pressure) were highlighted in animals exposed to artificial lighting, compared to those exposed to natural lighting.

These observations are consistent with the data of some other authors regarding impaired cardiovascular response under the influence of melatonin (Atkinson et al., 2005; Pandi-Perumal et al., 2016). A possible explanation of this is that in order to compensate for "sleepiness" associated with high morning melatonin concentrations, early morning exercise may require higher adrenergic stimulation to potentially offset melatonin effects (Kraemer et al., 2014).

Regarding the combined effect of lighting conditions and timing of exercise, the literature highlights the importance of phase-delaying effects. Continuous light exposure may alter nocturnal melatonin blood levels (Brown et al., 1991), and combining bright light (late in the evening) and exercise (early in the morning) produces significant additive phase-delaying effects (Youngstedt et al., 2016). Timing of exercise is important in obtaining phase-shifting effects, morning and evening exercise providing different effects on the circadian melatonin rhythm: morning and afternoon exercise may eventually enhance parasympathetic activity (Yamanaka et al., 2015), slowing the heart rate, while night exercise was associated with 1 to 2 hours phase delays, both in melatonin and TSH rhythm (Van Reeth, 1994). The loss of temporal variation in other hormones can also contribute to biological disorders, particularly in the case of those involving the hypothalamic-pituitary axis. The reduced variation of physical exercise, stress from the environment, and the thermal gradients that characterize modern lifestyle can reduce the autonomous dynamic range and induce a decrease of heart rate variability as well as a multitude of systemic dysfunctions (Yun et al., 2005).

The intensity of exercise is also correlated with plasma melatonin levels. It has been shown that short-term exercise acutely affects plasma melatonin levels in healthy individuals (Carr et al., 1981; Beck et al., 2016), depending on lighting during exercise, time of day, exercise intensity. An intense physical activity causes transient increases in plasma melatonin, in both sedentary and trained women; the melatonin level increased during all sessions of exercises and decreased toward the basal value when it was measured thirty minutes after the end of each exercise (Carr et al., 1981). Serum melatonin increases after exercise, but remains clearly below the night level (Ronkainen et al., 1986).

In our experiment, the most critical results were obtained in subjects supplemented with melatonin and trained in artificial lighting. Given the fact that exercise

was performed in the morning, the lowered/suppressed melatonin level which increases the immobility state and the imbalanced nervous vegetative and hormonal activity could also affect the cardiovascular response. Our results showed absent or lower statistical significance between groups I and II, supplemented with melatonin, for systolic and diastolic BP and mean BP (mm Hg). The explanation may reside in the moderate melatonin level as an ergogenic aid, particularly during the wakefulness period, and the timing of administration; for swimming rats, exercise tolerance is dependent on the time of day (Beck et al., 2016).

Globally, these results were contrary to what we expected, namely a positive correlation between artificial lighting, exercise and cardiovascular effects of melatonin supplementation. An ineffective dose, the duration of exposure or a possible impaired administration, or efficacy of MT1 and MT2 melatonin receptors could also lead to this result. Therefore, more extensive trials are needed to evaluate the role of exercise in relation to oxidative stress and melatonin effectiveness as a novel therapeutic intervention in cardiovascular diseases.

## **Conclusions**

1. Both natural and artificial lighting increased aerobic exercise capacity, though the latter in a more reduced manner.
2. Melatonin supplementation decreased aerobic exercise capacity under natural and artificial lighting conditions.
3. Artificial lighting, with and without melatonin supplementation, affected cardiovascular adaptation to exercise.

## **Conflicts of interests**

There are no conflicts of interests.

## **Acknowledgments**

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## **References**

- Arushanian EB, Baturin VA, Ovanesov KB. Characteristics of the combined action of melatonin and imizin on the structure of forced swimming and the circadian rhythm. *Biull Eksp Biol Med* 1989;107(6):709-711.
- Arushanian EB, Ovanesov KV. Characteristics of the psychotropic action of melatonin in relation to the dosage and time of day. *Farmakol Toksikol* 1989;52(6):33-37.
- Atkinson G, Barr D, Chester N, Drust B, Gregson W, Reilly T, Waterhouse J. Bright light and thermoregulatory responses to exercise. *Int J Sports Med* 2008; 29(3):188-193. doi: 10.1055/s-2007-965161.
- Atkinson G, Buckley P, Edwards B, Reilly T, Waterhouse J. Are there hangover-effects on physical performance when melatonin is ingested by athletes before nocturnal sleep? *Int J Sports Med* 2001;22(3):232-234.
- Atkinson G, Jones H, Edwards BJ, Waterhouse JM. Effects of daytime ingestion of melatonin on short-term athletic

- performance. *Ergonomics* 2005;48(11-14):1512-1522.
- Atkinson G, Edwards B, Reilly T, Waterhouse J. Exercise as a synchroniser of human circadian rhythms: an update and discussion of the methodological problems. *Eur J Appl Physiol* 2007; 99(4):331-341.
- Augustyniak A, Bartosz G, Čipak A, Duburs G, Horáková L, Łuczaj W, Majekova M, Odysseos AD, Rackova L, Skrzydlewska E, Stefek M, Strosová M, Tirzitis G, Venskutonis PR, Viskupicova J, Vranka PS, Zarković N. Natural and synthetic antioxidants: An updated overview. *Free Radic Res*, 2010;44(10):1216-1262. doi: 10.3109/10715762.2010.508495.
- Barbosa Dos Santos G, Machado Rodrigues MJ, Gonçalves EM, Cintra Gomes Marcondes MC, Areas MA. Melatonin reduces oxidative stress and cardiovascular changes induced by stanzolol in rats exposed to swimming exercise. *Eurasian J Med* 2013; 45(3):155-162.
- Beck WR, Botezelli JD, Pauli JR, Ropelle ER, Gobatto CA. Melatonin has an ergogenic effect but does not prevent inflammation and damage in exhaustive exercise. *Sci Rep* 2015;5:18065. doi: 10.1038/srep18065.
- Beck WR, Scariot PP, Gobatto CA. Melatonin is an ergogenic aid for exhaustive aerobic exercise only during the wakefulness period. *Int J Sports Med* 2016;37(1):71-76. doi: 10.1055/s-0035-1559698.
- Bicer M, Akil M, Baltaci AK, Mogulkoc R, Sivrikaya A, Gunay M, Akkus H. Protective effect of melatonin on lipid peroxidation in various tissues of diabetic rats subjected to an acute swimming exercise. *Bratisl Lek Listy* 2012; 113(12):698-701.
- Borges Lda S, Dermargos A, da Silva Junior EP, Weimann E, Lambertucci RH, Hatanaka E. Melatonin decreases muscular oxidative stress and inflammation induced by strenuous exercise and stimulates growth factor synthesis. *J Pineal Res* 2015;58(2):166-172.
- Brown GM, Bar-Or A, Grossi D, Kashur S, Johannson E, Yie SM. Urinary 6-Sulphatoxymelatonin, an index of pineal function in the rat. *J Pineal Res* 1991;10(3):141-147.
- Brown GM. Light, melatonin and the sleep-wake cycle. *J Psychiatry Neurosci* 1994; 19(5):345-353.
- Carocho M, Ferreira IC. A review on antioxidants, prooxidants and related controversy: Natural and synthetic compounds, screening and analysis methodologies and future perspectives. *Food Chem Toxicol* 2013;51:15-25. doi: 10.1016/j.fct.2012.09.021.
- Carr DB, Reppert SM, Bullen B, Skrinar G, Beitins I, Arnold M, Rosenblatt M, Martin JB, McArthur JW. Plasma melatonin increases during exercise in women. *J Clin Endocrinol Metab* 1981;53(1):224-225. DOI:10.1210/jcem-53-1-223.
- Dejica D. Antioxidanți naturali nenuționali. In: Dejica D. Antioxidanți și terapie antioxidantă. Ed. Casa Cărții de Știință, Cluj-Napoca, 2001, 135-137.
- Dominguez-Rodriguez A. Melatonin in cardiovascular disease. *Expert Opin Investig Drugs*. 2012;21(11):1593-1596. doi: 10.1517/13543784.2012.716037.
- Duffy JF, Czeisler CA. Effect of Light on Human Circadian Physiology. *Sleep Med Clin* 2009; 4(2):165-177. doi:10.1016/j.jsmc.2009.01.004.
- Gedikli S, Gelen V, Sengul E, Ozkanlar S, Gur C, Agirbas O, Cakmak F, Kara A. Therapeutic effects of melatonin on liver and kidney damages in intensive exercise model of rats. *Endocr Metab Immune Disord Drug Targets* 2015;15(4):308-314.
- Golombek DA, Burin L, Cardinali DP. Time-dependency for the effect of different stressors on rat pineal melatonin content. *Acta Physiol Pharmacol Ther Latinoam* 1992; 42(1):35-42.
- Hara M, Iigo M, Ohtani-Kaneko R, Nakamura N, Suzuki T, Reiter RJ, Hirata K. Administration of melatonin and related indoles prevents exercise-induced cellular oxidative changes in rats. *Biol Signals* 1997;6(2):90-100. doi:10.1159/000109113.
- Huertas MAC. Evaluación del estrés oxidativo/nitrosativo y hormonal y su relación con la eficiencia del entrenamiento en deportistas. Editorial de la Universidad de Granada, Granada, 2011.
- Ianăș O, Olinescu R, Bădescu I. Melatonin involvement in oxidative stress. *Endocrinologie* 1991;29(3-4):147-153.
- Kim E, Park H, Cha YS. Exercise training and supplementation with carnitine and antioxidants increases carnitine stores, triglyceride utilization, and endurance in exercising rats. *J Nutr Sci Vitaminol (Tokyo)* 2004; 50(5):335-543.
- Knight JA, Thompson S, Raboud JM, Hoffman BR. Light and Exercise and Melatonin Production in Women. *Am J Epidemiol* 2005; 162(11):1114-1122. doi:10.1093/aje/kwi327.
- Kraemer WJ, Boyd BM, Hooper DR, Fragala MS, Hatfield DL, Dunn-Lewis C, Comstock BA, Szivak TK, Flanagan SD, Looney DP, Newton RU, Vingren JL, Häkkinen K, White MT, Volek JS, Maresh CM. Epinephrine preworkout elevation may offset early morning melatonin concentrations to maintain maximal muscular force and power in track athletes. *J Strength Cond Res* 2014; 28(9):2604-2610.
- Langer M, Hartmann J, Turkof H, Waldhauser F. Melatonin in the human - an overview. *Wien Klin Wochenschr* 1997;109:707-713.
- Lee H, Kim S, Kim D. Effects of exercise with or without light exposure on sleep quality and hormone responses. *J Exerc Nutrition Biochem* 2014;18(3):293-299. doi: 10.5717/jenb.2014.18.3.293.
- Lee S, Park S, Won J, Lee SR, Chang KT, Hong Y. The incremental induction of neuroprotective properties by multiple therapeutic strategies for primary and secondary neural injury. *Int J Mol Sci* 2015;16(8):19657-19670. doi: 10.3390/ijms160819657.
- Leonardo-Mendonça RC, Martinez-Nicolas A, de Teresa Galván C, Ocaña-Wilhelmi J, Rusanova I, Guerra-Hernández E, Escames G, Acuña-Castroviejo D. The benefits of four weeks of melatonin treatment on circadian patterns in resistance-trained athletes. *Chronobiol Int* 2015;32(8):1125-1134. doi: 10.3109/07420528.2015.1069830.
- Maldonado MD, Manfredi M, Ribas-Serna J, Garcia-Moreno H, Calvo JR. Melatonin administered immediately before an intense exercise reverses oxidative stress, improves immunological defenses and lipid metabolism in football players. *Physiol Behav* 2012;105(5):1099-1103. doi: 10.1016/j.physbeh.2011.12.015.
- Marrin K, Drust B, Gregson W, Morris CJ, Chester N, Atkinson G. Diurnal variation in the salivary melatonin responses to exercise: relation to exercise-mediated tachycardia. *Eur J Appl Physiol* 2011; 111(11):2707-2714. doi: 10.1007/s00421-011-1890-7.
- Martoma A. Non-nutritional natural antioxidants. *Bull Transilvania Univ Braşov* 2009; 2:119-126.
- Mistraletti G, Umbrello M, Sabbatini G, Miori S, Taverna M, Cerri B, et al. Melatonin reduces the need for sedation in ICU patients: a randomized controlled trial. *Minerva Anestesiol* 2015;81(12):1298-1310.
- Morandi A, Brummel NE, Pandharipande P. Melatonin and the future of critically ill patients' outcomes. *Minerva Anestesiol* 2015;81(12):1277-1279.
- Nayanatara AK, Nagaraja HS, Anupama BK. The effect of repeated swimming stress on organ weights and lipid peroxidation in rats. *Thai J Physiol Sci* 2005;18(1):3-9.
- Ochoa JJ, Díaz-Castro J, Kajarabille N, García C, Guisado IM, De Teresa C, Guisado R. Melatonin supplementation ameliorates oxidative stress and inflammatory signaling induced by strenuous exercise in adult human males. *J Pineal Res* 2011;

- 51(4):373-380. doi: 10.1111/j.1600-079X.2011.00899.x.
- Pandi-Perumal SR, BaHammam AS, Ojike NI, Akinseye OA, Kendzerska T, Buttoo K, et al. Melatonin and human cardiovascular disease. *J Cardiovasc Pharmacol Ther*. 2016 pii: 1074248416660622. [Epub ahead of print].
- Pieri C, Moroni F, Marra M, Marcheselli F, Recchioni R. Melatonin is an efficient antioxidant. *Arch Gerontol Geriatr* 1995;20(2):159-165.
- Ponsford JL, Ziino C, Parcell DL, Shekleton JA, Roper M, Redman JR, Phipps-Nelson J, Rajaratnam SM. Fatigue and sleep disturbance following traumatic brain injury - their nature, causes, and potential treatments. *J Head Trauma Rehabil* 2012;27(3):224-233.
- Powers SK, DeRuisseau KC, Quindry J, Hamilton KL. Dietary antioxidants and exercise. *J Sports Sci* 2004;22(1):81-94.
- Reiter RJ, Richardson BA. Some perturbations that disturb the circadian melatonin rhythm. *Chronobiol Int* 1992;9(4):314-321.
- Reiter RJ. Antioxidant action of melatonin. In: Sies H (editor). *Antioxidants in Disease Mechanisms and Therapy*. San Diego: Acad. Press, 1997, 103-117.
- Ronkainen H, Vakkuri O, Kauppila A. Effects of physical exercise on the serum concentration of melatonin in female runners. *Acta Obstet Gynecol Scand* 1986; 65(8):827-829.
- Shebis Y, Iluz D, Kinel-Tahan Y, Dubinsky Z, Yehoshua Y. Natural Antioxidants: Function and Sources. *Food Nutr Sci* 2013;4(6):643-649.
- Staicu ML, Tache S. *Adaptarea organismului la efort fizic*. Vol. 2. Ed. Risoprint, Cluj-Napoca 2011, 183-191.
- Sun H, Gusdon AM, Qu S. Effects of melatonin on cardiovascular diseases: progress in the past year. *Curr Opin Lipidol* 2016;27(4):408-413. doi: 10.1097/MOL.0000000000000314.
- Surai PF. Silymarin as a natural antioxidant: an overview of the current evidence and perspectives. *Antioxidants* 2015;4(1):204-247. doi:10.3390/antiox4010204.
- Tache S. Capacitatea antioxidantivă a organismului. In: Dejița D. *Antioxidanți și terapie antioxidantă*. Ed. Casa Cărții de Știință Cluj-Napoca, 2001:50-51.
- Tamarkin L, Reppert SM, Klein DC, Pratt B, Goldman BD. Studies on the daily pattern of pineal melatonin in the Syrian hamster. *Endocrinol* 1980; 107(5):1525-1529. doi:10.1210/endo-107-5-1525.
- Troiani ME, Reiter RJ, Vaughan MK, Oaknin S, Vaughan GM. Swimming depresses nighttime melatonin content without changing N-acetyltransferase activity in the rat pineal gland. *Neuroendocrinol* 1988;47(1):55-60. doi:10.1159/000124891.
- Van Reeth O, Sturis J, Byrne MM, Blackman JD, L'Hermite-Balériaux M, Leproult R, Oliner C, Refetoff S, Turek FW, Van Cauter E. Nocturnal exercise phase delays circadian rhythms of melatonin and thyrotropin secretion in normal men. *Am J Physiol* 1994;266(6 PT 1):E964-974.
- Vingradova IA, Iliukha VA, Fedorova AS, Khizhkin EA, Unzhakov AR, Iunash VD. Age-related changes of exercise capacity and some biochemical indices of rat muscles under influence of different light conditions and pineal preparations. *Adv Gerontol* 2007;20(1):66-73.
- Voiculescu SE, Rosca AE, Zeca V, Zagrean L, Zagrean AM. Impact of maternal melatonin suppression on forced swim and tail suspension behavioral despair tests in adult offspring. *J Med Life* 2015;8(2):202-206.
- Vornicescu C, Boșca B, Crișan D, Yacoob S, Stan N, Filip A, Alina Sovrea. Neuroprotective effect of melatonin in experimentally induced hypobaric hypoxia. *Rom J Morphol Embryol* 2013;54(4):1097-1106.
- Yamanaka Y, Hashimoto S, Takasu NN, Tanahashi Y, Nishide SY, Honma S, Honma K. Morning and evening physical exercise differentially regulate the autonomic nervous system during nocturnal sleep in humans. *Am J Physiol Regul Integr Comp Physiol* 2015; 309(9):R1112-1121. doi: 10.1152/ajpregu.00127.2015.
- Yavari A, Javadi M, Mirmiran P, Bahadoran Z. Exercise-induced oxidative stress and dietary antioxidants. *Asian J Sports Med* 2015;6(1): e24898. doi: 10.5812/asjms.24898.
- Youngstedt SD, Kline CE, Elliott JA, Zielinski MR, Devlin TM, Moore TA. Circadian Phase-Shifting Effects of Bright Light, Exercise, and Bright Light + Exercise. *J Circadian Rhythms* 2016;14:2. doi: 10.5334/jcr.137.
- Yun AJ, Bazar KA, Gerber A, Lee PY, Daniel SM. The dynamic range of biologic functions and variation of many environmental cues may be declining in the modern age: implications for diseases and therapeutics. *Med Hypotheses* 2005; 65(1):173-178.
- \*\*\*. The Royal Commission on Environmental Pollution. *Artificial Light in the Environment*, 1<sup>st</sup> ed, Richmond, Surrey, UK: The Stationery Office Limited, 2009:9-22.