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# Melatonin and exercise
# Melatonina şi efortul fizic

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**Abstract**

Melatonin is the major hormone of the pineal gland which can influence the sleep-wake cycle. It is a highly lipophilic molecule able to prevent oxidative stress.

Exercise has been shown to affect plasma melatonin levels in humans and rodents. Plasma melatonin is increased during acute exercise sessions and can increase also after prolonged exercise. Melatonin concentration is an established marker of human circadian rhythmicity and physical activity is capable of inducing phase shifts in human circadian rhythms. Exercise-enhanced melatonin levels have a beneficial effect in several clinical conditions.

The melatonin administration confers protection against the oxidative damage caused by the severe oxidative stress imposed by exercise and may improve lipid profiles and exercise ability.

**Key words:** exercise effect, melatonin level, melatonin supplementation, exercise capacity.

**Rezumat**

Melatonina este hormonul major al glandei pineale, care poate influenţa ciclul somn-veghe. Este o moleculă foarte lipofilă, capabilă să prevină stresul oxidativ.

S-a demonstrat că efortul fizic afectează concentraţiile melatoninei plasmatice la om şi rozătoare. Nivelul melatoninei plasmatice a crescut în timpul sesiunilor de antrenament acut şi poate creşte, de asemenea, după un exerciţiu prelungit. Concentraţia melatoninei este un marker cunoscut pentru ritmul circadian uman, iar activitatea fizică este capabilă să inducă schimbări de fază în ritmul circadian uman. Concentraţiile crescute de melatonină induse de exerciţii au un efect benefic în mai multe condiţii clinice.

Administrarea melatoninei conferă protecţie împotriva leziunilor oxidative cauzate de stresul oxidativ sever indus de efortul fizic şi poate îmbunătăţi profilul lipidic şi capacitatea de efort.

**Cuvinte cheie:** efectul efortului, nivelul de melatonină, suplimentarea cu melatonină, capacitatea de efort.

## Melatonin synthesis and properties

Melatonin, N-acetyl-5-methoxytryptamine, is the major hormone of the pineal gland, although it has also been detected in other tissues.

Melatonin transmits information regarding the light-dark cycle, and retinal light exposure results in a suppression of melatonin (Van Cauter & Tasali, 2011). Melatonin can influence the sleep-wake cycle, by a sleep-promoting effect.

The factors influencing the secretion of melatonin are: the temporal variations of hormone secretion from the hypothalamic-pituitary axis in particular (Yun et al., 2005); environmental stressor agents (Yun et al., 2005); thermal gradients (Yun et al., 2005; McLellan et al., 2000); age (Vingradova et al., 2007); non-ionizing radiation (Reiter & Richardson, 1992); factors that alter sympathetic tone (Tannenbaum et al., 1989); exercise.

*Melatonin and the oxidant/antioxidant balance*

Melatonin is a highly lipophilic molecule that crosses cell membranes easily to reach subcellular compartments, including mitochondria, where it seems to accumulate in high concentrations and is able to prevent oxidative stress (Barbosa dos Santos et al., 2013).

Melatonin plays a direct primary protective role in oxidative stress, as a direct scavenger of hydroxyl radical (•HO) and superoxide anion radical ($O_2^{-\bullet}$), and also a secondary, indirect role, through the stimulation of glutathione peroxidase (GSH-Px) and superoxide dismutase (SOD), and through the inhibition of lipid

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peroxidation (Tache, 2001) and nitric oxide synthase (NOS) (Dejica, 2001).

Melatonin can maintain blood pressure and cardiac catalase activity (Barbosa dos Santos et al., 2013).

Studies have demonstrated its protective role against oxidative damage induced by drugs, toxins, and different diseases (Molpeceres et al., 2007).

Melatonin can also be pro-oxidant in concentrations below 0.25 mM in vitro (Ianas et al., 1991, cited by Dejica, 2001).

## Effects of exercise on melatonin levels

*Researches on animals*

Swimming depresses nighttime melatonin content without changing N-acetyltransferase activity in the rat pineal gland. The lack of change in the activities of the enzymes involved in melatonin synthesis and the contents of two melatonin precursors suggests that swimming depresses pineal melatonin content by enhancing melatonin efflux from the gland (Troiani et al., 1988).

*Researches in humans*

*a) Plasma melatonin levels*

*- Short-term exercise*

Short-term exercise has been shown to acutely affect plasma melatonin levels in healthy humans (Ronkainen et al., 1986; Carr et al., 1981): after a long-distance race, the concentration of melatonin was significantly increased after the competition (Ronkainen et al., 1986); in the study, after serial acute submaximal exercise tests performed during the course of a two-month progressive endurance training program, plasma melatonin increased during all exercise sessions and declined towards baseline values when re-measured thirty minutes after completion of each exercise (Carr et al., 1981). Also, in another study, melatonin levels were higher during exercise (aerobic exercise) than they were during the corresponding time in the control condition (Baehr et al., 2003).

In a study combining acute and regular exercise, initially untrained young women were subjected to periodic acute exercise testing during the course of an 8 week progressive aerobic exercise training program (training comprised cycle ergometry 2 days/week and running 4 days/week for increasingly prolonged periods of intense exercise eliciting 85% of maximum heart rate; acute exercise tests consisted of one-hour graded submaximal endurance rides on a bicycle ergometer). It was observed that during the rides, the plasma concentrations of melatonin rose significantly above baseline control values (Bullen et al., 1982).

The findings have been inconsistent due to differences in study designs, i.e. lighting during exercise, time of day, exercise intensity, as well as subject characteristics (Baehr et al., 2003).

*- Regular exercise*

Generally, a regular training program has low effects on melatonin level. In a study for the determination of the effect of regular exercise on melatonin secretion and excretion in young women, it was shown that sixteen weeks of exercise (150 min/week aerobic exercise for 4 months) had minimal effects on melatonin secretion in young women (Arikawa et al., 2013), but it is also possible that the duration and intensity of exercise training in this study was not sufficient to alter SNS activity and thus change melatonin levels.

Also, in another study, training did not cause any chronic changes in melatonin secretion, and the serum melatonin increases following physical exercise remained clearly below the nocturnal level (Ronkainen et al., 1986).

However, other studies have reported that prolonged exercise (a 28.5-mile high altitude race) in trained athletes can increase plasma melatonin and that this rise is not due to the concomitant opioid release (Strassman et al., 1989).

The effect of an exercise program on circadian rhythms is clearer. It is known that exercise at the time of high melatonin production rapidly depresses pineal concentrations of indole, without influencing its synthesis (Reiter & Richardson, 1992). Several studies have examined the effects of exercise on circadian rhythms. In mammals, the pineal gland transduces photoperiodic information to the neuroendocrine axis through nocturnal melatonin secretion (Poirel et al., 2003). The circadian rhythm of pineal melatonin is the best marker of internal time under low ambient light levels. Exogenous melatonin can act as a soporific, chronohypnotic, and/or chronobiotic agent (Cajochen et al., 2003).

Daytime sheltering, optical shading, and nighttime use of artificial light may reduce circadian luminal variation. The resulting melatonin alterations may contribute to systemic dysfunctions (Yun et al., 2005). Timing of exercise is important. Exercise at night has been shown to significantly blunt normal melatonin responses to dark cycles (Monteleone, 1990).

Exercise elicits phase shifts and acute alterations of melatonin that vary with circadian phase (Buxton et al., 2003). Even a single episode of physical activity is capable of inducing rapid phase shifts in human circadian rhythms; nighttime exercise is associated with 1- to 2-h phase delays of both melatonin and TSH rhythms (Van Reeth et al., 1994). In the exercise condition, all of the young subjects experienced delays in the circadian rhythm of melatonin, whereas in the older subjects there was slightly more variability in the response (Baehr et al., 2003). Subjects who completed three 45-min bouts of cycle ergometry each night showed a significantly greater shift in the dim light melatonin onset, dim light melatonin offset, and midpoint of the melatonin profile compared with non-exercising controls (Barger et al., 2004). The phase-shifting effects of exercise on the circadian system are preserved in older adults (Baehr et al., 2003). A longer duration of exercise exposure and/or repeated daily exposure to exercise may be necessary for reliable phase-shifting of the human circadian system; an early evening exercise of high intensity may induce phase advances relevant for the non-photic entrainment of the human circadian system (Buxton et al., 2003; Van Reeth et al., 1994).

The results of these studies indicated that exercise accelerated entrainment to the new sleep/dark schedule; exercise at night accelerated phase delays (Eastman et al., 1995; Schmidt et al., 1992), and daytime exercise accelerated phase advances (Miyazaki et al., 2001). Two studies used exercise in combination with bright light to phase delay circadian rhythms of young, healthy humans (Baehr et al., 1999; Youngstedt et al., 2002). Both studies found that exercise neither facilitated nor inhibited the phase shifts produced by bright light. Therefore, exercise may potentially be a useful treatment to help adjust circadian rhythms in older and young adults (Baehr et al., 2003), and the use of exercise can facilitate adaptation to shift work schedules and non-24-h schedules (Barger et al., 2004). However, in practical terms, the substantial levels of activity needed to obtain phase shifts may not be attainable by the majority of people. In mechanistic terms, the lack of agreement with the phase-shifting effects of bright light suggests that exercise is not exerting its effects via photic entrainment pathways. An alternative explanation may involve exercise-induced hyperthermia (Atkinson et al., 2007).

*b) Melatonin levels in saliva*

Salivary melatonin concentration is an established marker of human circadian rhythmicity. Melatonin is known to increase long-duration exercise, in which the body continuously works through the normal period of nighttime sleep, leading to altered circadian rhythms (Burgess, 2013).

In a study during a 36-hour endurance event, at the examination of saliva samples (melatonin determined via immunoassay), salivary melatonin concentrations followed typical light/dark oscillations throughout the race, but the melatonin levels were negatively correlated with the day of the race and positively associated with nighttime. Despite the prolonged sleep deprivation, the continuous stimulus of exercise was enough to attenuate an expected rise in melatonin during the second dark cycle of the 36-hour race (Davis et al., 2014).

In a study in male cyclists completing two evening cycling trials, it was found that the usual evening increase in melatonin was unaffected by exercise or post-exercise water immersion (Robey et al., 2013). The masking effect of moderate-intensity exercise on melatonin is approximately twice as high in the morning than the afternoon. The much steeper relationship between heart rate and melatonin changes in the morning raises the possibility that the time of day alters the relationships between exercise-mediated sympathetic nervous activity and melatonin secretion (Marrin et al., 2011).

## Effects of melatonin supplementation on exercise capacity

*Researches on animals*

There are several studies showing the beneficial effect of melatonin administration in exercise. It is well known that exercise (swimming) imposes a severe oxidative stress and enhances lipid peroxidation in the liver, muscle and brain. Pretreatment with melatonin and, to a lesser degree, other indolamines (5-methoxytryptamine, 5MT, and 6-hydroxymelatonin, 6HM) confers protection against oxidative damage associated with swimming for 60 min (Hara et al., 1997).

Antioxidant supplementation may improve lipid profiles and exercise ability in exercise-trained rats (Kim et al., 2004). In acute exercise, the increase in free radical production and the inhibition of antioxidant activity are both prevented by melatonin administration (Bicer et al., 2012).

However, there are also studies showing that melatonin applied from the age of 4 months did not influence exercise capacity in young rats. In mature and senescent animals, melatonin had stimulating effects on age-related physical activity, such as the reduction of exercise capacity depression and the normalization of antioxidant protection (Vingradova et al., 2007).

*Researches in humans*

Several studies in humans show the favorable antioxidant effect of melatonin during exercise. In a study in adult human males, which involved strenuous exercise, a physical test consisted of a constant run that combined several degrees of high effort (mountain run and ultra-endurance, with a total distance of the run of 50 km, with almost 2800 m of ramp in permanent climbing and very changeable climatic conditions); it was shown that melatonin supplementation lowered the levels of lipid peroxidation, with a significant increase in antioxidative enzyme activities, led to the maintenance of cellular integrity and reduced secondary tissue damage, had potent protective effects by preventing the over-expression of pro-inflammatory mediators and inhibiting the effects of several pro-inflammatory cytokines (Ochoa et al., 2011).

A study in football players showed that supplementation with 6 mg of melatonin administered 30 min prior to exercise significantly decreased lipid peroxidation products, lowered total antioxidant activity and triglyceride levels, and increased IgA levels 60 min after exercise. Therefore, the study concluded that melatonin administered immediately before intense exercise (acute sports exercise) reverses oxidative stress and improves immunological defense and lipid metabolism, which would result in an improvement in fitness (Maldonado et al., 2012).

Regarding the influence of melatonin on circadian rhythms, it was observed that the immediate effects of ingesting melatonin in the daytime include decreased alertness and body temperature (Atkinson et al., 2005). In a study that tried to improve sleep quality or alleviate symptoms of jet lag after transmeridian travel, athletes ingested 5 mg melatonin before sleep; the results showed that melatonin at this dose was unlikely to have any meaningful effects on physical performance in the morning after the subjects ingested the hormone (Atkinson et al., 2001).

Another study in physically active participants, aimed at examining whether daytime ingestion of melatonin led to impairments in variables relevant to short-term (<10 min) athletic performance, reported that the effects of 5 mg melatonin seemed more pronounced for the mental rather than physical components of short-term athletic performance, although cardiovascular response to exercise was affected. Some effects of melatonin were apparent 5 h after ingestion, when the hypothermic effects of melatonin had dissipated (Atkinson et al., 2005).

## Clinical applications of exercise effects on melatonin levels

In very serious diseases, such as cancer cachexia, there is a disruption in the rhythmic secretion of melatonin, an important time-conditioning effector. Studies have shown a tumor-dependent depression of serum melatonin in patients with prostate or breast cancer (Bartsch et al., 1994).

Exercise can be used as a complementary treatment strategy in chronic disease, due to its time-conditioning effect. Because exercise modulates the immune response through at least two different mechanisms - metabolic and neuroendocrine - the adoption of a regular exercise program as a complementary strategy in the treatment of cancer patients, with exercise bouts regularly performed at the same time of the day, will ameliorate cachexia symptoms and increase survival and the quality of life (Costa Rosa, 2004).

Exercise-enhanced melatonin levels may also contribute to impaired reproductive function in women engaging in endurance sports (Bullen et al., 1982).

Melatonin plus exercise had a synergistic effect on functional recovery after spinal cord injury; together they might create a microenvironment to facilitate proliferation of endogenous neural stem/progenitor cells (Lee et al., 2014).

The approaches aimed at strengthening circadian function, such as timed bright light and exercise, might potentially serve as complementary therapies for the non-motor manifestations of Parkinson's disease (Videnovic et al., 2014).

In athletic populations, melatonin and other nutritional interventions can be used as possible sleep inducers and represent promising potential interventions. The hormone melatonin and foods that have a high melatonin concentration may decrease the sleep onset time (Halson, 2014).

## Conclusions

1. Exercise affects plasma melatonin levels and is capable of inducing phase shifts in human circadian rhythms. Exercise-enhanced melatonin levels have a beneficial effect in several clinical conditions.

2. Melatonin supplementation confers protection against oxidative damage caused by exercise and may improve lipid profiles and exercise ability.

### Conflicts of interests
Nothing to declare

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