KOZŁOWSKA, Paulina, TABIAN, Alicja, SMĘT, Jakub, CHOJNACKA, Aleksandra Beata, BORAWSKI, Jacek, BURDON-SAJNÓG, Julia, SZYMONA-KUCEWICZ, Zofia, BARTELA, Klaudia Katarzyna, DUSIEL, Julia Katarzyna and WAŁACHOWSKA, Anna. The effect of melatonin supplementation on muscle recovery - a literature review. Journal of Education, Health and Sport. 2026;87:67463. eISSN 2391-8306.
https://doi.org/10.12775/JEHS.2026.87.67463
https://apcz.umk.pl/JEHS/article/view/67463

The journal has had 40 points in Minister of Science and Higher Education of Poland parametric evaluation. Annex to the announcement of the Minister of Education and Science of 05.01.2024 No. 32318. Has a Journal's Unique Identifier: 201159. Scientific disciplines assigned: Physical culture sciences (Field of medical and health sciences); Health Sciences (Field of medical and health sciences).
Punkty Ministerialne 40 punktów. Załącznik do komunikatu Ministra Nauki i Szkolnictwa Wyższego z dnia 05.01.2024 Lp. 32318. Posiada Unikatowy Identyfikator Czasopisma: 201159. Przypisane dyscypliny naukowe: Nauki o kulturze fizycznej (Dziedzina nauk medycznych i nauk o zdrowiu); Nauki o zdrowiu (Dziedzina nauk medycznych i nauk o zdrowiu). **© The Authors 2025;**
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The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 14.12.2025. Revised: 30.12.2025. Accepted: 30.12.2025. Published: 03.01.2026.

The effect of melatonin supplementation on muscle recovery – A literature Review

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Abstract

Introduction and objective: Melatonin is a hormone produced by the pineal gland that influences the synchronization of the circadian cycle. It is responsible for the proper functioning of the human biological clock by regulating the sleep–wake rhythm. The aim of this review is to present the current state of knowledge on the effects of melatonin supplementation on muscle regeneration after injuries, on muscle damage caused by ischemia and reperfusion, and on muscle recovery in older adults.

Review methods: All data were collected from publicly available sources. This article's databases were accessed via PubMed, BioMed Central.

A brief description of the state of knowledge: Recent studies show that melatonin, through it's influence on the human circadian cycle, also affects muscle regeneration. The biological clock coordinates the expression of many genes located in musce tissue that are responsible for muscle development, hypertrophy, metabolism and repair. In addition, the biological clock regulates glucose and lipid metabolism. Therefore, the proper functioning of the biological clock is important for muscle regeneration. Melatonin also exhibits strong antioxidant and anti-inflammatory effects, which protect against the harmful consequences of reperfusion. Moreover, melatonin influences the TGF-β1/Smad2/3 signaling pathway, thereby protecting against muscle fibrosis. Melatonin also increases the expression of the Pax7 protein in muscle cells, supporting the restoration of the satellite cell pool responsible for repairing damaged muscle.

Summary: Melatonin supplementation in athletes, older adults, and individuals who have experienced muscle ischemia and reperfusion may support muscle regeneration, thereby accelerating the patient's recovery and return to everyday life.

Keywords: melatonin, muscle regeneration, reperfusion, oxidative stress, biological clock, satellite cells, Pax7 protein, pathaway TGF-beta1/Smad2/3

Introduction

Physiology of Melatonin

Melatonin is a hormone produced mainly in the pineal gland. To a lesser extent, melatonin is also produced by the retina, lymphocytes, bone marrow, the gastrointestinal tract, and the

thymus.

Melatonin (N-acetyl-5-methoxytryptamine) is formed through the hydroxylation of tryptophan, which produces 5-hydroxytryptophan. Decarboxylation of 5-hydroxytryptophan results in 5-hydroxytryptamine, or serotonin. Acetylation of serotonin produces N-acetylserotonin, which is the direct precursor of melatonin. Finally, N-acetylserotonin is converted into melatonin through a methylation process.

The secretion of melatonin is regulated by the light–dark cycle. The highest melatonin levels are observed at night, when the activity of the enzyme N-acetyltransferase (NAT) increases 30- to 70-fold. Melatonin production and secretion peak during the night and decrease during the day. The peak plasma concentration of melatonin occurs around 3:00–4:00 a.m.

Melatonin exhibits high solubility in both lipids and water, which allows it to easily cross most cell membranes, including the blood–brain barrier. Once melatonin is released into the bloodstream, it distributes into various bodily fluids, cells, and tissues. About 70% of melatonin in the blood is bound to albumin, while smaller amounts are bound to orosomucoid or alpha-1-acid glycoprotein.

Melatonin production is absent or very low until around 3 months of age. Peak melatonin production occurs between 3 and 4 years of age. In adulthood, melatonin production decreases by approximately 80%.

Melatonin Receptors

Melatonin acts through endocrine, autocrine, and paracrine mechanisms. It can exert its effects by binding to a protein receptor, an intracellular protein, or orphan nuclear receptors, or it can act directly. Melatonin also interacts with protein molecules located inside cells. These protein molecules include calreticulin, calmodulin, and tubulin.

By binding to the family of orphan hormone receptors (RZR/ROR), melatonin exhibits immunomodulatory effects by stimulating the synthesis of IL-2 and IL-6 by nuclear cells.

Melatonin primarily acts through cell membrane-bound receptors that are coupled to G proteins (GPCRs).

The three main GPCR receptors are MT1, MT2, and MT3, along with one nuclear receptor. Melatonin receptors can be found in the aorta, the walls of the heart chambers, the brain, the cardiovascular system, cerebral and coronary arteries, the gallbladder, appendix, pancreas, liver, colon, parotid gland, platelets, kidneys, adipocytes, immune system cells, prostate epithelial cells, fetal kidneys, granulosa cells of the breast and ovaries, and the uterine muscle.

Melatonin engages various molecular pathways through the activation of membrane receptors: ML1, which has high affinity, and ML2, which has low affinity. ML1 has a direct effect on target cells and can also act via G protein-coupled receptors. ML1 includes two subtypes, MT1 and MT2. ML2 belongs to the family of quinone reductases.

The MT1 receptor in the blood vessels of the heart and in the suprachiasmatic nucleus helps modulate circadian rhythms and is responsible for the constriction of coronary blood vessels.
The MT2 receptor is mainly found in the retina, hippocampus, paraventricular nucleus, cerebellum, and cerebral cortex. This receptor is involved in circadian rhythm modulation, vasodilation, and participates in inflammatory responses.
Activation of the MT3 receptor inhibits leukocyte adhesion induced by leukotriene B4 and leads to a reduction in intraocular pressure.

Receptor-Independent Actions of Melatonin

A primary example of receptor-independent action of melatonin is free radical scavenging. Melatonin is a strong antioxidant; therefore, melatonin and its metabolites are responsible for eliminating free radicals. Melatonin also enhances the activity of antioxidant enzymes. Additionally, melatonin binds to transition metals, thereby preventing the formation of hydroxyl radicals.

Because melatonin is present in mitochondria, it protects proteins, lipids, and DNA from oxidative damage caused by free radicals. Melatonin's actions also include the regulation of complexes I and IV of the mitochondrial respiratory chain and the prevention of mutations and deletions in mitochondrial DNA.

In the brain, melatonin is responsible for regulating the circadian rhythm, seasonal adaptation, and the process of maturation. It has the ability to directly influence hippocampal neurons, which links it to memory. Melatonin also exhibits analgesic, anxiolytic, antidepressant, and

motor-regulating effects. Available studies also indicate that melatonin can support the treatment of disorders such as parkinsonism, Alzheimer's disease, brain edema, traumatic brain injury, cerebral ischemia, and gliomas.

Other significant actions of melatonin include neuroprotective effects, lowering blood pressure, pain modulation, anticancer activity, influence on reproductive development, and regulation of ovarian physiology.

Melatonin is responsible for regulating the secretion of GnRH from the hypothalamus, which in turn affects the synthesis of FSH and LH.

Skeletal Muscle Regeneration – Biological Mechanisms

We can distinguish two types of muscle: striated muscles and smooth muscles. Striated muscles are characterized by the presence of regularly arranged muscle fibers containing contractile proteins (actin and myosin). Because of the organized arrangement of myosin and actin proteins, the alternating light and dark bands visible in histological preparations of these muscles can be observed. Striated muscles include skeletal muscles and the heart muscle (myocardium).

Smooth muscles, on the other hand, do not have an organized, regular arrangement of contractile proteins; therefore, the characteristic striations are not visible in histological preparations.

Skeletal muscles are composed of multinucleated, spindle-shaped muscle cells, which usually extend between tendon attachments. A muscle cell (myocyte) typically corresponds to the length of the entire muscle. Between the basal lamina and the myocyte's cell membrane, there are satellite cells. When the muscle is undamaged, these cells remain in a quiescent state. When muscle injury occurs, satellite cells are activated, proliferate, and differentiate into myoblasts. Satellite cells contribute to the regeneration of damaged myocytes.

Inside the myocyte, we can distinguish muscle fibers, mitochondria, nuclei, and the sarcoplasmic reticulum. Peripheral endings consist of collagen fibers of the basal lamina, which form part of the tendon attachments of the muscle.

The sarcomere is the basic structural and functional unit of a muscle cell. It is a segment of a muscle fiber bounded on both sides by Z lines. The sarcomere is formed by molecules of the

protein alpha-actinin. Between the Z lines are the I band (isotropic) – light, and the A band (anisotropic) – dark.

The light I bands contain actin molecules and the troponin–tropomyosin protein complex. The dark A bands contain myosin molecules. Myosin filaments are located between actin filaments, which are arranged peripherally. The portion of the A band that does not contain actin filaments is called the H band.

Muscles in the human body retain the ability to regenerate in response to various stimuli that cause damage, which allows for the restoration of damaged muscle fibers.

The stages of muscle regeneration are:

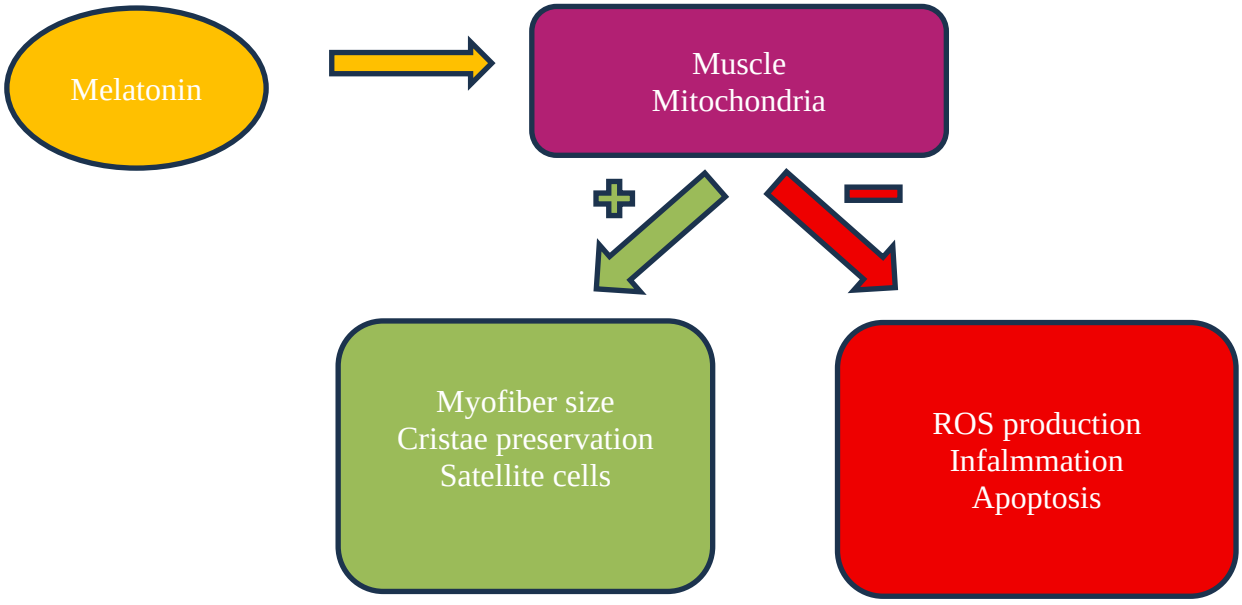
1. Degeneration
2. Inflammation
3. Regeneration
4. Maturation/Remodeling
5. Recovery of muscle function

As a result of injury, muscle fibers undergo degeneration/necrosis. This is followed by the formation of so-called sterile inflammation. During sterile inflammation, immune system cells infiltrate the site of damage. After the inflammatory response, the regeneration process is initiated. During regeneration, satellite cells and other stem cells are activated, proliferate, and differentiate.

The next stage is maturation and remodeling, during which minor restructuring of the muscle architecture occurs, along with matrix reorganization and angiogenesis. In the final stage, neuromuscular junctions are restored, which are essential for the recovery of muscle function.

Satellite cells (SCs) play a crucial role in the reconstruction of damaged muscle. They are located between the basal lamina and the sarcolemma of muscle fibers and exist in a mitotically quiescent state.

Satellite cells transition from a quiescent state to an active state when they are needed for the growth and repair of damaged muscle.



Pic.1 Melatonin and mitochondria.

The Influence of Circadian Rhythm and Sleep on Regeneration

The circadian rhythm is responsible for regulating fundamental physiological processes, including muscle regeneration, protein synthesis, and cellular homeostasis. Disruption of the circadian rhythm also impairs muscle function, particularly in older adults. Additionally, age-related declines in muscle mass and regenerative capacity contribute to sarcopenia.

The circadian rhythm coordinates essential life processes such as the sleep–wake cycle, hormone secretion, and metabolic homeostasis. Muscle regeneration, which involves the repair and rebuilding of damaged muscle tissue, is a crucial factor in maintaining muscle health.

Skeletal muscle tissue possesses an internal biological clock. This clock coordinates the expression of many genes in muscles, including genes involved in processes such as muscle development, hypertrophy, metabolism, and repair. The biological clock in muscles also regulates glucose and lipid metabolism, ensuring the availability of energy substrates when needed to support muscle activity. The circadian clock also participates in the repair of muscle tissue and regeneration after injury or physical exercise.

The muscle clock is also responsible for maintaining insulin sensitivity, enabling cells to respond to insulin and take up glucose from the bloodstream. Additionally, it regulates glucose absorption by muscle cells. These functions are supported by a well-functioning circadian rhythm in muscles, which helps prevent metabolic disorders and allows for optimal energy utilization by the body.

Disruption of the muscle clock can impair muscle function and repair, contributing to a decrease in muscle mass and strength. Impaired muscle clock function may reduce the tissue's ability to operate efficiently and regenerate effectively.

Properties of Melatonin Relevant to Muscle Regeneration

Melatonin possesses strong antioxidant and anti-inflammatory properties, making it a protective agent against the harmful effects of reperfusion.

Melatonin directly scavenges free radicals, which are harmful by-products of oxygen metabolism. It also activates endogenous antioxidant enzymes, including glutathione peroxidase and superoxide dismutase, thereby strengthening the cellular defense system. Melatonin acts synergistically with other antioxidants, such as vitamin E and glutathione, enhancing their protective effects.

Melatonin also has other properties important for muscle regeneration. It can modulate inflammatory pathways, which are crucial in ischemic and rheumatic injuries. This hormone inhibits the production of pro-inflammatory substances and cytokines, reducing the inflammatory response and supporting tissue repair. Additionally, melatonin exhibits immunomodulatory effects, preventing excessive activity of immune system cells and thereby limiting further tissue damage by regulating the immune response.

Melatonin plays a very important role in various inflammatory processes as a broad-spectrum free radical scavenger. This makes it a promising therapeutic agent for musculoskeletal disorders. Available studies report that administering melatonin at a dose of 100 mg per day led to a decrease in serum levels of lipid peroxidation (LPO), nitrites and nitrates, as well as advanced oxidation protein products (AOPP). These effects were observed

in athletes engaged in resistance training, helping to prevent oxidative damage to skeletal muscles caused by physical exertion.

The study also demonstrated that melatonin treatment prevents apoptosis of undifferentiated C2C12 cells in the presence of hydrogen peroxide. This protective effect is attributed to the stimulation of expression and activity of antioxidant enzymes.

Inhibition of TGF-β Signaling by Melatonin

Available studies conducted on mice indicate that melatonin inhibits the TGF-β1/Smad2/3 signaling pathway in aging muscles and stem cells. This may help protect against fibrogenic conversion and muscle fibrosis.

Additionally, a study demonstrated that melatonin is capable of restoring the satellite cell pool in aged mice. With age, the number of satellite cells decreases, contributing to impaired muscle maintenance. The levels of the Pax7 protein were examined in aged mice and in young control mice. Pax7 levels were lower in the older mice. After melatonin supplementation in the aged mice, this difference was partially reduced. Western blot analysis showed that melatonin administration increases Pax7 protein expression in muscle tissue. These findings indicate that melatonin can restore the satellite cell pool in aged mice.

Activation of the AMPK Pathway by Melatonin

In the available literature, a study conducted on mice examined the effects of melatonin on skeletal muscle injury. It was observed that melatonin supports mitochondrial function by activating the AMPK/PGC-1α signaling pathway. This activation leads to increased activity of respiratory chain complexes I, II, and IV, enhanced ATP synthesis capacity, increased mtDNA replication, and reduced ROS levels.

The researchers used an AMPK inhibitor to determine the specificity of the pathway. The AMPK inhibitor blocked melatonin’s regulatory effect on muscle fiber phenotype. This study confirmed that the AMPK/PGC-1α pathway is a primary target of melatonin, revealing a mechanism by which melatonin induces regeneration of slow-twitch muscle fibers by influencing mitochondrial metabolic pathways.

Discussion

The results of available studies indicate that melatonin plays a multifaceted role in muscle regeneration after injury. Melatonin affects muscle regeneration at both the cellular and functional levels. Studies on animal models and C2C12 muscle cells have shown that melatonin increases the expression of the Pax7 protein, which is a critical marker of satellite cells. This promotes the proliferation and differentiation of satellite cells into myotubes, facilitating the reconstruction of muscle fibers after damage.

Another very important action of melatonin is its anti-inflammatory and antioxidant effect. This activity reduces inflammation and cell death in regenerating muscles. Melatonin lowers levels of oxidative stress markers and enhances the antioxidant capacity of tissues, while also limiting leukocyte infiltration and apoptosis.

Another important function of melatonin is its effect on proper mitochondrial function and energy metabolism. Administration of melatonin activates the AMPK/PGC-1α pathway, leading to improved mitochondrial function in regenerating muscle fibers, increased ATP production, and enhanced regeneration of slow-twitch fibers. Consequently, melatonin treatment after injury not only improves muscle morphology but also increases muscle strength, as confirmed by a study on rats with muscle injury.

Comparing the results of available studies on the effects of melatonin on muscle regeneration, it is evident that melatonin acts synergistically at multiple levels. Melatonin modulates satellite cells, reduces oxidative stress and inflammation, and also improves the energetic function of muscles.

Most of the available studies use animal or cell models, which limits their translational relevance to humans. Therefore, further clinical research is necessary to evaluate the effectiveness of melatonin in muscle regeneration after injury and in pathological conditions. Determining the optimal dose and timing of administration will also be essential.

Melatonin appears to be a promising compound that can support muscle regeneration through its multifaceted actions, ultimately leading to increased muscle strength and function.

Conclusions:

Melatonin exhibits anti-inflammatory and antioxidant effects, which reduce muscle cell apoptosis and leukocyte infiltration, thereby accelerating the reconstruction of muscle fibers and improving their morphology. By stimulating satellite cells, melatonin supports muscle regeneration after injury. Satellite cells are activated through increased expression of myogenic markers, such as Pax7. Melatonin supplementation also enhances mitochondrial function and energy metabolism via activation of the AMPK/PGC-1α pathways. The therapeutic potential of melatonin in muscle regeneration is promising; however, further clinical studies are needed to determine effective doses, timing of administration, and safety in humans.

Disclosures

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All authors have read and agreed with the published version of the manuscript.

Funding Statement:

The study did not receive special funding.

Institutional Review Board Statement:

Not applicable.

Informed Consent Statement:

Not applicable.

Data Availability Statement:

Not applicable.

Acknowledgments:

Not applicable.

Conflict Of Interest:

The author declare no conflict of interest.

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