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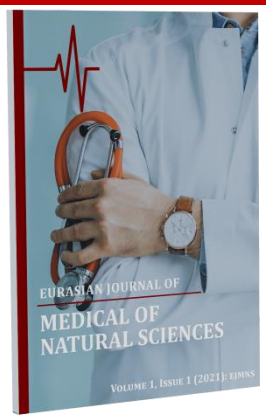

CIRCADIAN RHYTHMS, CHRONONUTRITION, PHYSICAL TRAINING, AND REDOX HOMEOSTASIS—MOLECULAR MECHANISMS IN HUMAN HEALTH

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ABSTRACT

A wide range of physiological processes, human behaviors, and social interactions are intricately regulated by the dynamic interaction between external factors and the body's internal circadian rhythms. This complex regulatory system is prone to disturbances, and in modern society, misalignment between circadian rhythms and environmental cues is common, often linked to negative health outcomes. Many of today's most prevalent chronic diseases are closely associated with changes in lifestyle, including reduced physical activity, exposure to artificial light (commonly referred to as light pollution), sedentary habits coupled with consumption of energy-dense foods, irregular eating patterns, disrupted sleep (in both quality and duration), shift work, and social jetlag. The rapid pace of modern life and domestic routines has far outstripped the rate of genetic adaptation, leaving circadian rhythms vulnerable to multiple disruptions, increasing susceptibility to disease. This review aims to synthesize current research that supports the integration of circadian rhythms, molecular homeostasis, oxidative stress, and the effects of physical activity, sleep, and nutrition.

1.Introduction

Scientific research has established the critical role of the circadian system in regulating essential biological processes, including homeostasis, cardiovascular function, and glucose metabolism. Disruptions to the circadian clock, which can manifest as disturbances or a loss of rhythmicity, are now recognized as significant contributors to various diseases and accelerated aging, highlighting their importance as major health concerns.

In the realm of physiological regulation, redox reactions involving reactive oxygen and nitrogen species play a key role, governing processes such as cellular signaling and immune responses. However, oxidative stress, caused by an imbalance in these reactions, can disrupt cellular signaling and lead to harmful modifications of important biomolecules like DNA,

proteins, and lipids. Notably, a two-way relationship exists between circadian rhythms and oxidative stress. Disruptions in circadian rhythms can significantly affect redox biology, while changes in redox homeostasis can, in turn, impact the regulation of circadian processes. For example, important antioxidant enzymes such as superoxide dismutase (SOD), glutathione peroxidase (GSH-Px), and catalase (CAT) display distinct circadian patterns in their expression and activity.

This interaction between circadian rhythms and redox biology has emerged as a fascinating area of study in human health. Physical exercise, recognized as a powerful environmental signal, not only offers health benefits but also has the potential to correct circadian disturbances. Interestingly, the body's response to exercise can vary based on circadian timing. Furthermore, research on the relationship between exercise, reactive species, and oxidative stress has revealed that the oxidative species produced during exercise can have both positive and negative health effects, depending on the type, intensity, and duration of the exercise.

The connection between circadian rhythms and redox metabolism, particularly in relation to exercise, nutrition, and sleep, is a newly emerging field of study.

2. Circadian Rhythms in the Regulation of Human Physiological and Behavioral Processes

Biological rhythms refer to predictable cycles of physiological and behavioral changes in living organisms. These internal rhythms can continue independently of external cues, although they consistently interact with and adapt to environmental changes. In humans, a complex network of biological signaling systems, including the immune system, gastrointestinal system, and central nervous system, operates in coordinated rhythmic patterns. These rhythms are vital for maintaining overall homeostasis and balance within the body. They are classified based on their cycle duration into three types: circadian rhythms (about 24 hours), ultradian rhythms (shorter than 24 hours, often lasting seconds to minutes), and infradian rhythms (longer than 24 hours).

The central biological clock, located in the suprachiasmatic nucleus (SCN) of the hypothalamus, controls most circadian rhythms in mammals. The SCN functions as the body's "master clock," generating circadian rhythms through a negative feedback loop involving clock genes. To synchronize this central pacemaker with the 24-hour day-night cycle, external signals called zeitgebers, such as light, are essential. Light is the most important environmental cue for circadian entrainment, with the retinohypothalamic tract acting as the primary pathway for transmitting light signals.

Measuring circadian physiology presents challenges due to the influence of external factors like sleep-wake cycles and internal circadian rhythms. The SCN, which regulates the circadian pacemaker, can be affected by numerous external and internal factors such as light exposure, temperature, dietary patterns, physical activity, and stress, making it difficult to isolate its role in observed rhythmic phenomena.

Melatonin is a commonly used marker for measuring circadian phase, as its levels are less affected by other biochemical and physiological factors. Blood melatonin levels typically rise a few hours before the onset of sleepiness, just before nighttime sleep in healthy individuals. This increase is known as the dim light melatonin onset (DLMO), and saliva is

often used to measure it since salivary melatonin levels closely correlate with plasma melatonin levels. For accurate measurements, participants must stay in dim light, avoid physical activity and certain foods before saliva collection, and, depending on the study design, collect hourly saliva samples over a 24-hour period to create a partial melatonin curve.

2.1. The Circadian Clock and Sleep Homeostasis

The interaction between the circadian clock and sleep homeostasis is described by the "two-process model," which illustrates how these systems regulate sleep. Sleep is controlled by two key physiological processes: process S (the homeostatic process) and process C (the circadian process), which work in opposition to regulate wakefulness and sleep patterns. Process S, much like hunger or thirst, builds up sleep pressure during wakefulness and decreases it during sleep. Adenosine, a byproduct of cellular activity, accumulates in the brain during wakefulness, activating adenosine receptors, leading to increased sleepiness and reduced alertness. Conversely, during sleep, adenosine levels decrease, resulting in reduced receptor activation and heightened alertness.

The circadian process (process C) governs the 24-hour rhythm of sleep and wakefulness and is primarily influenced by melatonin, which is responsive to light and dark exposure, but can also be modulated by other external factors like food and physical activity. The quality and timing of sleep over a 24-hour cycle are determined by the interplay between processes C and S. When process S is high, and process C is low, sleep quality and probability improve. However, conditions such as depression or sleep phase disorders can disrupt this balance, leading to insomnia or non-restorative sleep. Additionally, caffeine, an adenosine receptor antagonist, temporarily enhances alertness, but chronic use can lead to receptor upregulation, diminishing its effectiveness and potentially requiring intermittent breaks to sustain its wake-promoting effects.

2.2. The Influence of Circadian Rhythms on Human Cognitive and Physical Performance

The circadian rhythm significantly influences physical and cognitive performance, with performance variability increasing as task complexity rises. This daily performance rhythm oscillates between 10% and 30% of the daily average, emphasizing the importance of carefully considering the timing of athletic performance. Research has shown that daily rhythmic fluctuations affect a variety of physiological and behavioral functions that influence athletic performance, including baseline sensory-motor skills, psychomotor functions, and perceptual factors. Studies also suggest that variables such as workload, physiological stress, motivation, arousal levels, chronotype, environmental lighting, sleep patterns, and the "post-lunch dip" phenomenon can modulate the circadian rhythm's effect on athletic performance.

Numerous human studies have highlighted the significant impact of circadian rhythms on cognitive and physical functioning. One study, which utilized a 20-hour forced desynchrony protocol, found a circadian pattern in psychomotor vigilance, short-term memory, calculation, digit-symbol substitution, and alertness tests, with peak performance occurring near the time of highest core body temperature (CBT), just before melatonin secretion begins. Conversely, a significant performance decline was observed around the time

of lowest CBT, just after melatonin levels peak. Furthermore, cognitive performance declined with extended periods of wakefulness, even after controlling for circadian influences.

Early chronobiological studies explored diurnal variations in performance-related abilities, including elbow flexion strength, reaction time, information processing rate, physiological tremor, and eye-hand coordination. Freivalds et al. found that performance ratings were generally higher during the day and evening than at night or in the morning, despite relatively small fluctuations. Similarly, Teo et al. examined the circadian patterns of cortisol and testosterone in relation to strength and power performance across four different times of the day. The study revealed that peak power output occurred at 16:00, with no significant correlation between power output and cortisol or testosterone levels.

Although these studies had limitations, such as not using constant routine or forced desynchrony techniques and having limited data collection points, they support the conclusion that cognitive and physical performance tend to be better in the late afternoon compared to the morning, likely due to the influence of the circadian pacemaker.

2.3. The Relationship Between Circadian Rhythms and Exercise: Performance and Health Benefits

Recent research has provided valuable insights into the connections between physical training, circadian alignment, and biological signals that emerge during exercise. The circadian clock can be synchronized by both photic (light-related) and non-photic stimuli such as temperature, physical activity, and food intake. Given that exercise imposes significant challenges to the body's balance, affecting cellular, tissue, and organ systems, modern theories have begun to explore the relationship between exercise and circadian rhythms in terms of performance and health benefits. A growing body of evidence suggests that exercise can influence the circadian system in rodents, and emerging data in humans indicate that exercise can shift circadian phases, possibly influenced by individual chronotypes. Exercise appears to be a powerful factor in synchronizing both central and peripheral clocks, including those in skeletal muscle. For example, male rugby players exhibit significantly higher expression of core-clock genes compared to sedentary individuals.

Consequently, researchers and clinicians are increasingly interested in the idea that exercise might mitigate the negative health effects of circadian misalignment and that there may be an optimal time to exercise for maximizing its therapeutic benefits. Among all peripheral tissues, skeletal muscle is particularly responsive to circadian clock activity.

Molecular clocks regulate the transcription of many clock-controlled genes, either directly through the actions of core transcription factors CLOCK and BMAL1, or indirectly via other clock-regulated proteins. This coordination establishes rhythmic patterns of gene expression, which in turn govern various biological processes under circadian control. The CLOCK and BMAL1 heterodimer also rhythmically initiates the expression of their transcriptional repressors, Period (Per1 and Per2) and Cryptochrome (Cry1 and Cry2).

Studies have demonstrated that the molecular clock plays a critical role in regulating glucose metabolism in skeletal muscle. For instance, deleting BMAL-1 in mouse skeletal muscle leads to impaired glucose uptake, reduced levels of GLUT-4, and disruption of key glycolytic enzymes. These disruptions suggest that alterations in the molecular clock within muscle tissue may contribute to the development of metabolic conditions such as type 2

diabetes. Since exercise is widely recommended for the prevention and treatment of type 2 diabetes, it appears that the metabolic benefits of exercise are partly achieved through its effects on the molecular clock in muscle, helping to restore local circadian regulation. This is supported by findings showing increased gene and protein expression of BMAL-1 and PER2 in skeletal muscle of adults with obesity and pre-diabetes after 12 weeks of exercise training, alongside improvements in body composition, insulin sensitivity, and maximal oxygen uptake. Notably, BMAL-1 gene expression was positively correlated with glucose disposal rate.

While exercise clearly benefits skeletal muscle metabolism, little is known about how the timing of exercise influences the magnitude of these effects. This is important because the biological clock drives daily rhythms in human skeletal muscle metabolism. Mitochondrial oxidative capacity, a key determinant of exercise performance, follows a daily rhythm, peaking in the late evening and reaching its lowest point in the early afternoon. Given that oxidative capacity is crucial for exercise performance, it is unsurprising that studies report significant time-of-day effects on exercise performance, capacity, and strength, with some variations linked to the daily expression patterns of the PER2 gene. These fluctuations in performance are thought to be driven by circadian changes in core body temperature, hormone levels, neuromuscular function, and metabolic activity. Body temperature, which tends to peak in the late afternoon, plays a key role in these performance variations. Since exercise-induced thermoregulation also follows a circadian rhythm, this may explain differences in fatigue onset during similar activities performed at different times of day, particularly during endurance exercises. Studies have shown that exercise efficiency is higher in the late afternoon compared to the early morning, likely due to clock-driven variations in metabolic processes, particularly carbohydrate metabolism, which requires less oxygen, a lower heart rate, and reduced perceived exertion. In the context of competitive and elite sports, understanding the connection between exercise capacity and the molecular clock could be useful for optimizing training and competition schedules, though this concept is not entirely new.

Aligning exercise with other chronobiological strategies—such as time-restricted eating, optimized sleep patterns, and chronotype assessment—offers an appealing approach to maximizing the metabolic and health benefits of physical activity.

2.4. Circadian Regulation of Glucose Metabolism

In glucose metabolism, factors such as insulin and cortisol follow patterns of expression and secretion that are synchronized with circadian rhythms, much like the main organs involved in glucose regulation—liver, pancreas, adipose tissue, and muscles. Glucose tolerance is highest during the day and decreases at night. Insulin production is influenced by both feeding-fasting cycles and circadian rhythms, with nutrient levels in the blood signaling insulin release, also regulated by the circadian system and the suprachiasmatic nucleus (SCN).

Pancreatic β-cells receive parasympathetic input, which is regulated by GABAergic projections from the SCN. The SCN also influences the liver through glutamatergic and GABAergic pathways, affecting glucose production. Although the peak functional period of pancreatic β-cells remains unclear, some studies suggest that they may function optimally around midday, potentially enhancing postprandial glucose control when carbohydrates are

consumed during this time. Cortisol, a steroid hormone crucial for metabolism and stress response, also follows a daily rhythm, peaking at the start of the active phase.

Circadian clocks respond to environmental cues, with light being the most powerful signal for the SCN clock. Food intake and patterns of activity and rest serve as important zeitgebers for peripheral clocks that regulate local physiological processes. Proper synchronization of these peripheral clocks is essential for coordinated bodily functions. Disruptions in circadian rhythms can lead to metabolic disturbances, causing a range of issues from fatigue and irritability to chronic conditions like obesity, type 2 diabetes, cardiovascular disease, and inflammation.

2.5. The Role of Exercise in Entrainment of Circadian Rhythms: Experimental and Clinical Evidence

Exercise acts as a non-photic stimulus that can help entrain circadian clocks. In studies conducted on rodents kept in constant darkness, it was found that exercise could shift the phase of circadian rhythms associated with wheel-running behavior. Specifically, changes in the expression of Per1 and Per2 genes in the SCN were observed in response to wheel-running activity in constant darkness. Additionally, the timing of exercise plays a role in regulating circadian clocks. For example, wheel running at the beginning of the active phase has a stronger effect on reducing Per2 gene expression amplitude in the SCN compared to exercise at the end of the active phase. Scheduled exercise has been shown to entrain molecular clocks in peripheral tissues like skeletal muscles and lungs, although not the SCN, especially under light-dark conditions. Furthermore, scheduled exercise was found to entrain Per2 gene expression in the submandibular gland, suggesting that planned physical activity can synchronize molecular clocks in both the SCN and peripheral tissues, though its ability to reset the master clock is limited without light exposure.

Similar phase-shifting effects of exercise on circadian rhythms have also been observed in humans. Studies have shown that exercise can accelerate phase delays in circadian rhythms induced by forced sleep changes. For instance, in one study, plasma melatonin levels were used to track circadian rhythms, and bicycle ergometer exercise under dim light helped to facilitate the 9-hour sleep-schedule-induced phase delay of the circadian melatonin rhythm. Additionally, exercise was found to differentially affect the circadian melatonin rhythm and the sleep-wake cycle in humans. Exercise accelerated the re-entrainment of the sleep-wake cycle, particularly under dim light and a phase-advanced sleep schedule, though it did not significantly affect the melatonin rhythm in the same conditions. Another study investigating the effects of exercise on circadian melatonin rhythms and sleep-wake cycles under bright light with an 8-hour phase-advanced sleep schedule found that while the sleep-wake cycle was entrained by the sleep schedule alone, exercise helped advance the melatonin rhythm. These findings suggest that the combination of light exposure and exercise serves as a powerful cue for entraining circadian rhythms in humans.

3. Chrononutrition: The Relationship Between Circadian Rhythms, Nutrients, and Meal Timing

Recently, there has been growing interest in the complex interaction between dietary factors and the circadian system, a concept referred to as chrononutrition. "Chrononutrition" highlights the intricate relationship between the timing of food intake, meal composition, and

the body's circadian rhythms, all of which significantly influence metabolic health. This concept emphasizes that in addition to the type and amount of food consumed, the timing of meals plays a crucial role in overall well-being. It proposes an "optimal" eating schedule that aligns with the body's metabolic rhythms to promote better health.

Unlike daylight variations, which are determined by geographical location, changes in food intake and meal timing can significantly impact nutrient-sensing pathways that maintain homeostasis. Synchronizing meal timing, quality, and quantity with metabolic rhythms throughout the day can optimize metabolism and promote overall health. Various neurotransmitters regulate the sleep-wake cycle, including 5-hydroxytryptophan, serotonin, melatonin, gamma-aminobutyric acid (GABA), orexin, acetylcholine, galanin, noradrenaline, and histamine. As a result, nutritional interventions that target these neurotransmitter systems may positively influence sleep patterns. Dietary precursors have the potential to affect the synthesis and functionality of neurotransmitters. For instance, serotonin synthesis depends on the availability of its precursor, tryptophan, in the brain. Tryptophan crosses the blood-brain barrier via a system shared with other large neutral amino acids (LNAA). The ratio of tryptophan to LNAA in the bloodstream is crucial for tryptophan's transport into the brain and can be increased through the consumption of tryptophan-rich foods, a high-carbohydrate/low-protein diet, or the intake of α-lactalbumin, a protein derived from whey.

3.1. The Interconnected Roles of Tryptophan, Serotonin (5-HT), Physical Activity, Sleep, and Dietary Habits

The neurotransmitter serotonin (5-HT) plays a key role in regulating a wide range of physiological functions, including mood, sleep patterns, pain perception, and meal timing. In the context of physical activity, 5-HT is involved in the development of central fatigue through various biochemical pathways. The synthesis of 5-HT depends on the availability of tryptophan, an essential amino acid, with cortisol acting as a key regulator of tryptophan hydroxylase, the enzyme responsible for 5-HT synthesis. Unlike the synthesis of noradrenaline and dopamine, which are not affected by changes in tyrosine levels, tryptophan levels directly impact 5-HT synthesis because the enzyme is not saturated with its substrate, tryptophan. Higher plasma levels of free tryptophan can increase 5-HT concentrations in neurons. Studies have shown that elevated free tryptophan levels can boost 5-HT concentrations by 35% in the brains of exercising rats. Tryptophan crosses the blood-brain barrier via a carrier protein for large neutral amino acids (LNAA) (Figure 1).

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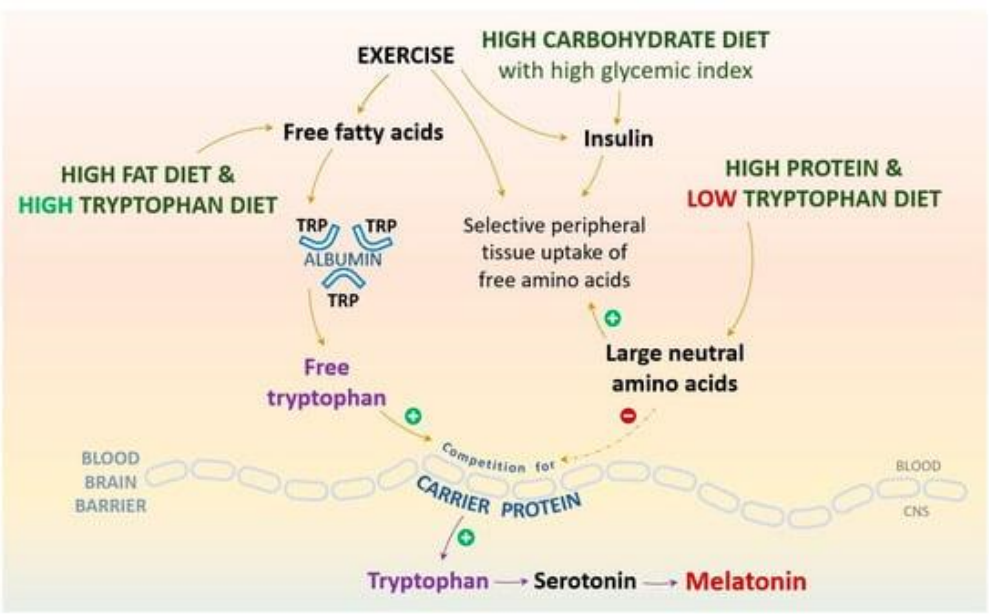

Figure 1. The increase in melatonin production can be achieved through various nutritional interventions that aim to enhance tryptophan (Trp) availability at the CNS level. Generally, this process can be realized by either increasing free Trp availability or reducing the relative plasma concentration of large neutral amino acids (LNAA). The passage of tryptophan through the blood–brain barrier constitutes a multifaceted process, as the active transport of amino acids to the brain, performed by a particular carrier protein, is accessible to all LNAA and is not exclusive to tryptophan. So, tryptophan must engage in competition with other LNAA, which are often more abundantly available in the food supply, to secure transport into the brain. To augment the availability of tryptophan for serotonin and melatonin synthesis, it is advantageous to redirect these competing amino acids toward peripheral tissues. This diversion can be facilitated through the release of insulin, which in turn fosters protein synthesis in muscle tissue. Notably, the process of insulin shunting effectively diminishes the pool of LNAA that reach the brain, thereby liberating transporters for tryptophan binding. In light of this mechanism, the co-consumption of carbohydrates in conjunction with tryptophan-rich foods holds the potential to enhance the entry of tryptophan into the brain. These objectives can also be accomplished by adopting a high-protein diet richer in tryptophan compared to LNAA, consuming carbohydrates to elevate the free Trp-to-branched-chain amino acid (BCAA) ratio and stimulate insulin release, which facilitates BCAA uptake into muscle. Additionally, melatonin production can be influenced by the consumption of high-fat meals, leading to increased free fatty acids and subsequently higher free Trp levels. Furthermore, engaging in physical exercise can impact both free fatty acids and insulin levels, contributing to the intensification of melatonin synthesis.

From a nutritional standpoint, the intake of large neutral amino acids (LNAA), particularly tyrosine and branched-chain amino acids (BCAA), affects tryptophan's transport into the brain and its subsequent conversion to serotonin and melatonin. The process of tryptophan crossing the blood-brain barrier is complex, as the active transport system for amino acids applies to all LNAA, not just tryptophan. To enhance tryptophan availability for serotonin and melatonin synthesis, it is beneficial to divert the competing amino acids toward

peripheral tissues. This can be achieved by stimulating insulin release, which promotes protein synthesis in muscle tissue. Given this mechanism, consuming carbohydrates alongside tryptophan-rich foods can increase tryptophan's entry into the brain. As a result, this dietary approach can enhance the synthesis of serotonin and melatonin. Manipulating blood LNAA levels through specific dietary choices can lead to significant variations in brain tryptophan availability, affecting serotonin and melatonin synthesis rates, which in turn influences mood, cognitive function, sleep-wake cycles, and the secretion of hormones like prolactin and cortisol.

Consuming a mixture of LNAA, particularly BCAA, reduces the rate of tryptophan transport to the brain and decreases serotonin synthesis. While this may improve physical performance by reducing serotonin availability, the effects are generally considered modest. However, it is important to note that BCAA consumption also lowers tyrosine transport and dopamine synthesis in the brain. Combining BCAA with tyrosine could potentially prevent the decline in dopamine levels while still lowering serotonin production.

From the physical activity perspective, BCAA are required by active muscles during exercise, reducing competition for tryptophan at the blood-brain barrier, thus increasing tryptophan entry into the brain. Additionally, physical activity induces a lipolytic effect, which mobilizes free fatty acids in the plasma, displacing albumin-bound tryptophan and further increasing the amount of free tryptophan available to the brain. These processes may contribute to central fatigue during exercise. Fatigue could also result from slight reductions in glucose or oxygen levels, which may affect brain metabolism during physical activity, although this is unlikely in the case of glucose. While tryptophan supplementation has shown cognitive benefits, it has not consistently been proven to reduce fatigue during exercise.

3.2. Melatonin: Regulator of Cellular Redox Homeostasis, Circadian Rhythms, and the Sleep-Wake Cycle

Melatonin, scientifically known as N-acetyl-5-methoxytryptamine, is an endogenous indoleamine that plays a key role in regulating a variety of physiological processes. These include the regulation of circadian rhythms, the sleep-wake cycle, anxiety, immune responses, and cardiac function. Melatonin also affects appetite and helps regulate insulin levels, among other important functions. Notably, melatonin and its metabolites are powerful antioxidants, effectively neutralizing reactive oxygen species (ROS) and reactive nitrogen species (RNS), protecting mitochondria from oxidative stress. Additionally, melatonin and its derivatives enhance the activity of several antioxidant enzymes, helping to maintain cellular redox balance and playing a crucial role in the aging process (Figure 2).

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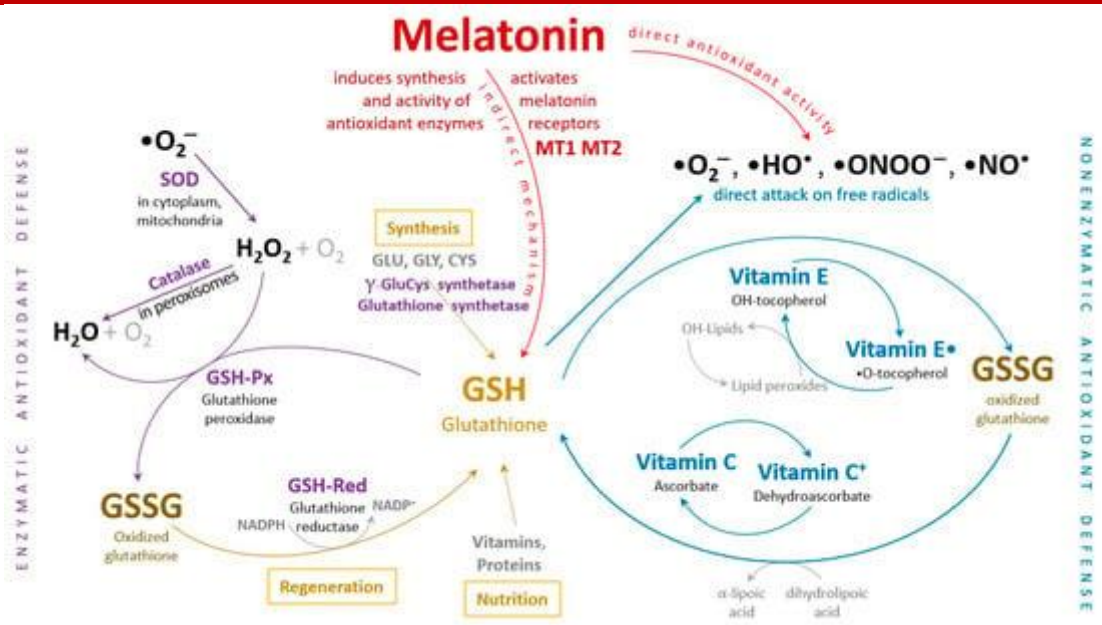

Figure 2. The human organism's antioxidant defense mechanism involves a cooperative interaction between enzymatic and non-enzymatic antioxidant systems to collectively shield the cells and organ systems from harm caused by free radical damage. ROS—reactive oxygen species, SOD—Superoxide dismutase, GSH—reduced glutathione, GSSG—oxidized glutathione, GSH-Px—Glutathione peroxidase, GSH-R—Glutathione reductase.

Disruptions in cellular redox balance can be triggered by certain conditions, such as intense physical activity, as well as unhealthy lifestyle behaviors like smoking, alcohol consumption, poor diet, and exposure to environmental factors such as radiation, viruses, and bacteria. Intense and prolonged exercise can lead to inflammation due to the excessive production of free radicals, ROS (reactive oxygen species), and RNS (reactive nitrogen species), potentially causing oxidative damage to muscle tissues. However, regular moderate-to-vigorous exercise generates a moderate amount of ROS/RNS, triggering beneficial adaptive responses that help prevent and manage diseases linked to oxidative stress. In the context of sports, maintaining redox balance in skeletal muscle is particularly important, as it relies on the efficiency of ROS generation.

Additionally, recent evidence suggests that physical exercise can influence melatonin secretion in both the short and long term, with effects occurring within 12 to 24 hours. The mechanism by which reduced sleep affects glucose metabolism is thought to be complex and involves several factors, including reduced brain glucose utilization, changes in sympatho-vagal balance, increased evening cortisol levels, prolonged nighttime growth hormone release, and the activation of pro-inflammatory pathways.

Leptin and ghrelin are key hormonal regulators of appetite, with leptin suppressing food intake and ghrelin stimulating it. Numerous studies have shown that sleep deprivation lowers leptin levels and increases ghrelin levels, leading to heightened hunger and cravings, particularly for carbohydrate-rich foods, following sleep restriction. Beyond changes in appetite-regulating hormones, sleep deprivation also negatively affects the hypothalamic-pituitary-adrenal (HPA) axis and the hypothalamic-pituitary-gonadal (HPG) axis. This leads to an increase in catabolic hormones like cortisol and alterations in anabolic hormone secretion,

such as testosterone and insulin-like growth factor 1. These hormonal shifts may impair protein synthesis and enhance muscle breakdown, hampering muscle recovery after intense physical activity.

As the body transitions from wakefulness to sleep, autonomic balance shifts towards parasympathetic dominance. Sleep is associated with reduced sympathetic activity and lower levels of catecholamines, whereas sleep deprivation leads to increased sympathetic activity and higher catecholamine levels. Additionally, sleep loss has been shown to reduce the responsiveness of hormones like adrenocorticotropic hormone (ACTH), adrenaline, noradrenaline, and serotonin. Over time, these changes can lead to altered stress system responsiveness, similar to what is observed in mood disorders.

4. Physical Activity, Hormones, and Mood Interconnections

Physical activity has been shown to trigger biological responses from various endocrine glands, influencing the release and action of hormones. These hormones—such as growth hormone, thyroxine, cortisol, and reproductive hormones—play a role in mood regulation. Endocrine effects can alter receptor density on target neurons or affect neurotransmitter synthesis, metabolism, and release, thereby impacting mood.

4.1. Thyroid Hormones

The link between mood disorders and thyroid disorders is often attributed to the effects of thyroid hormones on adrenergic receptor synthesis. Elevated thyroid hormone levels can increase adrenergic "tone" in the brain, as β-adrenergic receptors serve as postsynaptic receptors for noradrenaline. Physical activity can lead to an increase in free T4 levels, likely due to a higher concentration of free fatty acids in the blood, which displaces T4 from its binding proteins. While T4 is an active hormone, the increase in free T4 levels during exercise does not appear to serve any particular physiological function. Instead, increased TSH levels and activation of the hormonal release axis would be expected. These hormonal changes during physical activity are a result of the body's increased energy demands. The consistently elevated free T4 levels in individuals who exercise may heighten feelings of alertness caused by noradrenergic brain activity.

4.2. Adrenocorticotropic Hormone (ACTH), Cortisol, and Growth Hormone

ACTH stimulates the adrenal cortex to release cortisol, which is secreted alongside β-endorphin (βE) in response to stress. Both ACTH and β-endorphin are derived from the precursor protein proopiomelanocortin (POMC), with ACTH stimulating the stress hormone system, while βE helps counterbalance it due to its calming effects. Cortisol receptors, located in various parts of the brain, are linked to mood and behavior.

Cortisol release is triggered by physiological stress, and physical exercise has a significant impact on plasma cortisol levels. During exercise, the sympathetic nervous system is activated, leading to ACTH release, which then prompts cortisol secretion into the bloodstream. Prolonged aerobic exercise, especially at higher intensities, causes a greater increase in cortisol compared to resistance training of similar intensity and duration. Factors such as age, gender, fitness level, exercise intensity, and type all contribute to an individual's cortisol response pattern. Elevated cortisol levels indicate muscle breakdown, which increases the risk of muscle loss, particularly in older adults. Cortisol production changes with age and responds differently to exercise intensities between males and females. Although

cortisol increases with exercise duration and intensity, this rise is not consistent across all intensities. Higher intensities and longer durations are the key factors driving cortisol production, increasing the potential for muscle breakdown.

Besides physical activity, sleep is another critical factor in regulating cortisol synthesis. In modern social and work environments, acute sleep deprivation and circadian misalignment are common. Studies show that acute total sleep deprivation and chronic circadian misalignment affect cortisol levels differently. A single night of total sleep deprivation elevates cortisol levels, especially in the early evening and morning, while weeks of circadian misalignment result in reduced cortisol levels throughout the day. Stress levels increase following acute sleep deprivation, but chronic circadian misalignment does not significantly affect stress ratings compared to a well-aligned control group. Chronic circadian misalignment, however, raises levels of anti-inflammatory cytokine IL-10 and pro-inflammatory proteins like TNF-α and C-reactive protein (CRP), especially during waking hours. The balance between TNF-α and IL-10 shows minimal changes during circadian misalignment. These findings suggest that acute sleep deprivation triggers a stress response characterized by elevated nighttime cortisol, while chronic circadian misalignment results in physiological adaptation with reduced cortisol levels and increased inflammation.

The rhythms of growth hormone (GH) and cortisol are strongly influenced by sleep patterns, which are, in turn, affected by physical activity. Both hormones exhibit significant surges during intense exercise, and it takes several hours for their levels to return to baseline. While GH and cortisol levels rise considerably during exercise, they play secondary roles in regulating glucose and fat metabolism, with catecholamines and insulin taking precedence. Nevertheless, these hormones are essential during exercise and in the recovery period. GH release follows a circadian pattern, with peaks occurring at night. Although closely tied to slow-wave sleep, GH levels remain high during nighttime wakefulness. Beyond circadian rhythms, factors like age, gender, nutrition, sleep habits, body composition, and fitness level influence GH secretion at rest and during exercise.

Both continuous and intermittent exercise lead to increased GH levels within the first 15–20 minutes of activity. However, the GH response may be diminished if a high-fat meal is consumed before exercise, whereas a high-glucose meal has a lesser impact on the GH response. This suggests that pre-exercise meal composition can modulate hormonal responses to exercise, influencing its anabolic and lipolytic effects. In addition to their metabolic and endocrine roles, cortisol and GH can affect behavior: mood and alertness levels influence one's ability to engage in physically demanding activities, which is critical for performance. Circadian fluctuations in emotional states may also impact teamwork and communication in group settings, such as coaching and team sports.

4.3. Insulin

Physical activity also affects insulin levels, with plasma insulin levels decreasing for at least a day following a single workout. This reduction in insulin is primarily due to an increase in plasma free fatty acids, which accelerates lipolysis and reduces the inhibition of hormone-sensitive lipase in adipose tissue. The rise in free fatty acids in the plasma also elevates the levels of free fractions of T4, steroid hormones, and tryptophan—the precursor of serotonin. While lower glucose levels have been associated with negative emotional states, the brain's

glucose supply during physical activity is sufficient to maintain its function, indicating minimal effects on mood during or after exercise.

4.4. Leptin

Leptin, a hormone derived from adipose tissue, is another endogenous molecule significantly influenced by physical activity. As body fat decreases, leptin levels tend to drop in individuals who engage in regular sports activities. However, acute sessions of moderate exercise typically do not cause significant changes in mean leptin plasma levels, given the individual variability. A more substantial reduction in leptin is generally seen only after intense physical activities, such as running a marathon. Leptin levels, like many hormones, fluctuate throughout the day, which can affect measurements taken after exercise. Neuropeptide Y (NPY), a neurotransmitter, is inhibited by leptin and helps regulate food intake patterns. While leptin may be related to anxiety, the NPY-Y1 receptor (associated with anxiety) and the receptor involved in food regulation function in different ways.

5. The Dual Roles of Reactive Oxygen and Nitrogen Species: Beneficial and Harmful Effects

Throughout evolutionary processes, organisms have developed a variety of protective mechanisms to manage excessive levels of reactive oxygen species (ROS), leading to what is commonly referred to as oxidative stress. Oxidative stress refers to elevated intracellular ROS levels, which can damage lipids, proteins, and DNA—an issue long associated with numerous human diseases.

The mechanisms responsible for ROS production (such as aerobic respiration or the activity of flavin-containing oxidases) and their rapid elimination (through enzymes like catalase) are present in almost all cell types, maintaining a dynamic equilibrium under normal physiological conditions. However, this balance can be disrupted by excessive ROS production, often linked to pathological conditions, or exposure to external substances like pollutants or drug metabolites, as well as by insufficient production or activity of protective systems. The effects of oxidative stress depend on the extent of cellular damage caused by ROS and how the cell responds. If the damage cannot be repaired, or if both internal and external antioxidant defenses fail to neutralize the ROS-induced harm, the cell may suffer irreversible damage (Figure 3).

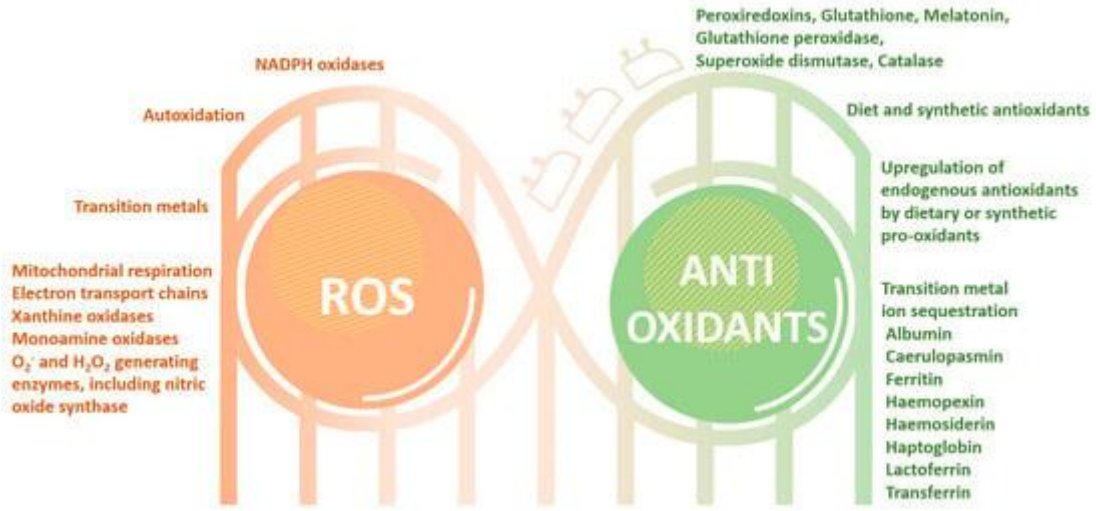

Figure 3. The physiologic continuous process of reactive oxygen species (ROS) generation is counterbalanced by a plethora of antioxidant enzymatic and non-enzymatic mechanisms, whose modulation signals are finely orchestrated and intimately interconnected.

Despite their potential for harm, ROS also play essential roles as secondary messengers, transmitting extracellular signals to generate specific cellular responses. For example, at physiological nanomolar levels, hydrogen peroxide acts as a key signaling molecule, modulating crucial protein targets involved in metabolic regulation and stress response pathways. These coordinated events enable cells to adapt to changing environments and stressors. In addition to hydrogen peroxide, other reactive species like nitric oxide, hydrogen sulfide, and oxidized lipids are also involved in redox signaling. Extensive research has greatly expanded our understanding of oxidative stress and the complex mechanisms governing ROS production and regulation, as well as their crucial role in cellular signaling processes.

5.1. The Role of Reactive Oxygen and Nitrogen Species in Maintaining Biological Homeostasis

Reactive oxygen species (ROS) are highly reactive molecules, including radicals such as O2• and OH•, and non-radical oxygen derivatives like H2O2. These molecules are vital in cellular signaling and are essential for maintaining homeostasis in biological systems. ROS are generated through interactions of O2• with other molecules, resulting in hydrogen peroxide and hydroxyl radicals, which can interconvert with reactive nitrogen species (RNS) and have similar effects. The primary source of ROS is often attributed to inefficient electron transfer in the mitochondrial respiratory chain, but various enzymatic and non-enzymatic processes also contribute to ROS production.

Nitrosative stress is closely related to oxidative stress, with ROS, including superoxide anions, singlet oxygen, hydroxyl radicals, hydrogen peroxide, peroxynitrite, and nitric oxide, playing key roles. Peroxynitrite (ONOO−), formed during oxidative stress, can modify biomolecules such as proteins, lipids, and DNA through nitration, leading to the formation of 3-nitrotyrosine (3-NT). Tyrosine nitration, a post-translational modification caused by interactions with RNS/ROS, is a hallmark of nitrosative stress. Recent studies have identified 3-NT as a specific biomarker of nitrosative stress, providing valuable insights into tracking intracellular ONOO− production, its location, and the extent of cell damage.

All oxygen-utilizing cells engage in oxygen metabolism, or cellular respiration, which produces ROS as a natural byproduct of aerobic processes. Exogenous factors like metals, redox cycling compounds, radiation, chemotherapy, carcinogens (such as estrogenic compounds), and various dietary and environmental influences can also lead to ROS generation. Elevated ROS levels often trigger nonlinear cellular responses. In both normal and pathological conditions, there is a delicate balance between oxidant and antioxidant systems that regulate ROS production, distribution, and deactivation.

The key systems for ROS detoxification involve a range of endogenous antioxidants, such as catalase, glutathione, thioredoxin-related compounds, and superoxide dismutase, along with exogenous antioxidants like reduced glutathione, carotenoids, and vitamins C and E. However, redox balance can easily be disrupted, often tipping in favor of oxidants and shifting ROS levels from physiological to potentially harmful ranges, resulting in oxidative and nitrosative stress.

5.2. The Impact of ROS Overproduction on the Pathogenesis and Progression of Chronic Diseases

Oxygen and the regulation of circadian rhythms are vital components of numerous physiological processes that maintain homeostasis. These processes include regulating blood pressure, managing sleep-wake cycles, and fine-tuning cellular signaling pathways, all of which play a critical role in health and disease progression.

When the body or its cells are exposed to significant stress, their ability to regulate internal systems—such as maintaining redox balance and circadian patterns—can become compromised. This disruption occurs at both cellular and organismal levels and can lead to a range of adverse outcomes, including the onset and progression of chronic diseases like cardiovascular disorders, neurodegenerative diseases, and cancer.

An increase in ROS levels can be triggered by various factors, such as sedentary behavior, sleep deprivation, consumption of processed foods, exposure to chemicals, alcohol and toxin ingestion, and long-term overuse of medications. When the balance between the antioxidant defense system and ROS production is disrupted, it significantly influences the development of conditions like diabetes, metabolic syndrome, heart attacks, strokes, sleep disorders, cognitive and physical decline, inflammatory conditions, and DNA damage-related cancers (Figure 4).

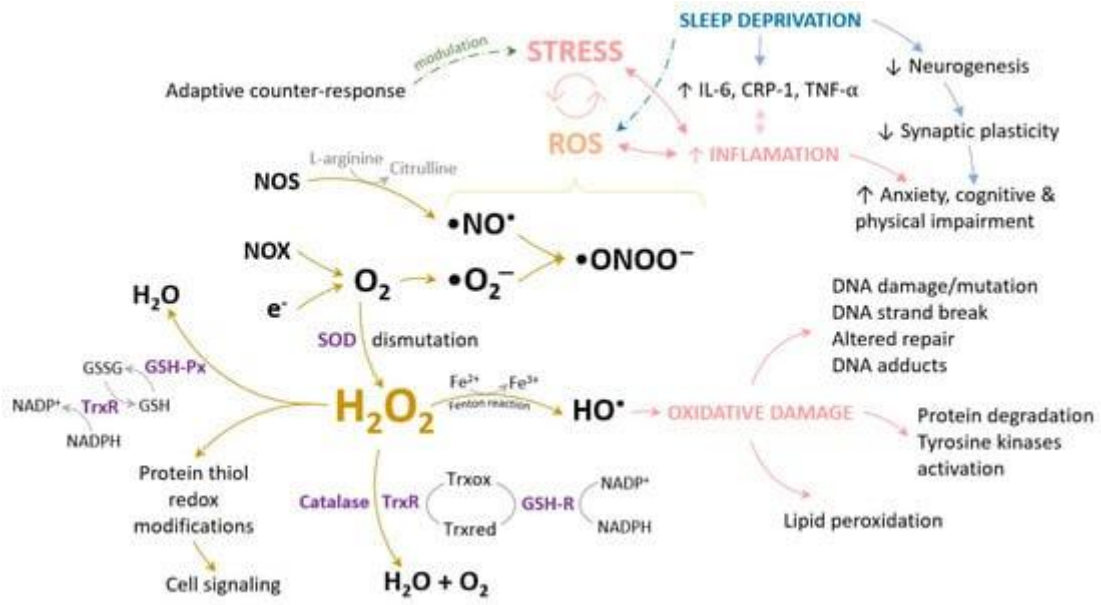

Figure 4. The generation of reactive species is at the same time a physiologic and a pathological process, dictated by the disequilibrium between the amount produced and the extent to which they are neutralized by active antioxidant mechanisms. The signaling processes involving reactive oxygen species (ROS) occupy a pivotal position in the control of proinflammatory mechanisms, protein redox adjustments, cellular proliferation, and apoptotic cell death. The safeguarding of cellular and tissue integrity against the detrimental effects of elevated ROS concentrations is effectively mediated by the actions of antioxidant defense enzymatic and non-enzymatic factors. *ROS—reactive oxygen species, IL-6—interleukin 6, CRP-1—C reactive protein, TNF-α—Tumor necrosis factor-alpha, NOS—Nitric oxide synthase, NOX—NADPH oxidases, SOD—Superoxide dismutase, GSSG—oxidized glutathione, GSH—*

reduced glutathione, GSH—Px-Glutathione peroxidase, TrxR—Thioredoxin reductase, GSH-R—Glutathione reductase.

These defense mechanisms, primarily based on antioxidant protection, employ a variety of strategies that involve both enzymatic and non-enzymatic components. Notable non-enzymatic antioxidants include glutathione (GSH), vitamins such as C and E, selenium, carotenoids, thioredoxins (Trx), lipoic acid (ALA), and flavonoids. Alongside these, the activity of cellular antioxidant enzymes forms a critical line of defense against ROS. Key enzymes include superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GSH-Px), the reduced-to-oxidized glutathione ratio, and glutathione transferase (GST). Their primary role is to protect tissues from oxidative damage caused by oxygen radicals, both by preventing the formation of ROS and by neutralizing them into inactive compounds.

6. Physical Exercise as a Key Factor in Oxygen Dynamics in the Human Body

Oxidative stress is a well-known consequence of physical exercise, even after a single workout session, with the generation of free radicals being a key indicator of the body's muscular and systemic response to activity. This conclusion is supported by decades of exercise research. Physical activity increases oxygen demand, particularly in skeletal muscles, which alters blood distribution to different organs. Additionally, exercise-induced muscle damage attracts neutrophils and macrophages to the affected area. These physiological changes from acute exercise enhance free radical production and lead to oxidative modifications in biomolecules. Recent advances in biochemical and molecular techniques have revealed that free radicals also play a role in the physiological adaptations that follow exercise training. Therefore, the effects of exercise-induced free radicals can be both beneficial and harmful, depending on the duration and intensity of the training, forming the basis of a hormetic response.

Hormesis is the concept where exposure to low levels of a potentially harmful agent or environmental factor induces beneficial adaptive effects on cells or organisms. This principle is central to the ideas of "conditioning" and "adaptation". These concepts suggest that moderate stress activates or enhances existing cellular and molecular pathways, enabling cells and organisms to better handle greater stressors. Hormesis explains how exercise conditions the body and promotes long-term adaptations: moderate physical activity is linked to reduced disease risk and lower mortality, while excessive activity can increase these risks.

During exercise, the body encounters various homeostatic disruptions, including thermal, metabolic, hypoxic, oxidative, and mechanical stress. For older individuals with compromised antioxidant defenses or chronic low-grade inflammation, antioxidant supplements and non-steroidal anti-inflammatory drugs (NSAIDs) may help preserve or enhance muscle adaptation. However, in younger individuals, such interventions could reduce the exercise-induced improvements in insulin sensitivity and muscle protein synthesis. Therefore, the effects of these interventions can vary between different groups of people engaging in physical activity.

Recent interest has focused on applying stress to skeletal muscles at different stages of exercise to promote a more extensive adaptive response in the body. This stress can be induced through methods like limiting carbohydrate intake, using blood flow restriction with low-intensity isometric or eccentric contractions, cryotherapy, or heat exposure.

6.1. Signaling Pathways in Exercise-Induced Oxidative Stress

Endurance exercise training generates oxidants in skeletal muscles and activates enzymatic antioxidant mechanisms, upregulating the expression and activity of key antioxidant enzymes like SOD1, SOD2, GSH-Px, and CAT in skeletal muscles. Studies have shown that endurance training enhances total SOD activity in oxidative type I (soleus) and IIa (red gastrocnemius) muscle fibers. Consistent endurance training also increases both cytosolic and mitochondrial GSH-Px activity in oxidative skeletal muscle fibers. Furthermore, endurance training boosts CAT activity in the peroxisomes and mitochondria of highly oxidative muscles.

Exercise-induced oxidative stress triggers mitochondrial biogenesis, a process driven by repeated muscle contractions. Newly formed mitochondria are highly efficient and produce fewer ROS for the same amount of ATP. Proteins involved in mitochondrial biogenesis, such as PGC-1α, NRF-1, and mitochondrial transcription factor A, are upregulated with consistent exercise. However, mitochondria are not the only source of ROS during muscle contraction—superoxide activity in the cytosol increases with muscle contraction, followed by a delayed rise in the mitochondria, with NADPH oxidases (NOX) also identified as contributors to superoxide production. Research has shown that ROS generation increases in isolated mitochondria following muscle contraction compared to a relaxed muscle sample.

Moderate ROS levels are crucial in signaling pathways related to mitochondrial biogenesis, and reduced ROS-stimulated mitochondrial biogenesis correlates with lower PGC-1α expression. Antioxidant supplementation with vitamin C and other antioxidants (vitamin E, A, polyphenols) lowers ROS levels and prevents the activation of enzymatic antioxidant mechanisms. Reduced PGC1α expression is associated with lower activity of all antioxidant enzymes, which form the first line of defense against oxidative stress.

Muscle fatigue is caused by damage to muscle fibers due to ROS generation. However, it has become clear that small amounts of ROS can trigger the transcription of important genes involved in the body's antioxidant defense system. Muscle fatigue and oxidative damage are positively correlated, which presents an opportunity for dietary therapies aimed at improving exercise performance. Given the protective effects of antioxidants in reducing muscle damage caused by intense exercise, antioxidant supplementation may be a useful strategy for individuals engaging in prolonged athletic activities.

Conclusions

Recent advancements in molecular biology have highlighted the connection between circadian rhythms and redox dynamics, especially in the context of promoting or evaluating physical activity for health benefits. Redox reactions are now recognized as a fundamental part of cellular signaling, functioning alongside other biochemical processes that precisely regulate human metabolism. This review emphasizes that specific nutrients, when consumed in the right proportions and timing, can offer antioxidant benefits, enhance stamina, and improve sleep, underscoring the importance of tailored nutritional interventions based on age and gender. Additionally, personalized exercise regimens designed to strengthen homeostatic mechanisms can further promote health, improve sleep quality, boost energy expenditure, and optimize exercise adaptations in both general and athletic populations. These approaches

deserve more exploration as effective tools for enhancing quality of life and physical performance.

Beyond light, physical activity plays a critical role in synchronizing environmental oscillators through the master biological clock. This synchronization initiates a cascade of physiological responses involving hormones, enzymes, and neurotransmitters, creating a complex network regulated by multiple feedback loops.

Since an organism's adaptability heavily depends on its internal biological clock, which is influenced by environmental factors, clinical interventions should carefully consider each patient's circadian patterns, oxidative profile, nutritional and sleep needs, physical activity levels, and age and gender factors. The evidence suggests that sleep quality, chrononutritional strategies, time-specific physical activity, and intrinsic circadian rhythms have a profound impact on overall bodily functions, maintaining homeostasis.

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