

Circadian Rhythms and Chronotherapy: Integrating Molecular and Physiological Mechanisms into Physiotherapy and Rehabilitation Sciences

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Introduction

Defining Circadian Rhythms and Adaptive Value

Circadian rhythms (CRs) are defined as endogenously generated biological timing mechanisms that repeat with a period of approximately 24 hours (derived from the Latin *circa diem*) and are present in virtually all organisms (Patel et al., 2022). These internal biological cycles confer a profound adaptive advantage by enabling organisms to anticipate and prepare for predictable cyclical environmental shifts, such as the availability of light and nutrients (Patel et al., 2022). This predictive capacity is critical for survival and maximizing energy efficiency.

The role of CRs in physiological regulation is comprehensive, ensuring the temporal separation (temporal partitioning) of essential biochemical, metabolic, and redox processes at the cellular level (Patel et al., 2022). Furthermore, CRs regulate almost every systemic function within the body, including the cardiovascular, metabolic, endocrine, and immune systems (Cermakian & Boivin, 2009). These rhythmic oscillations also play a central role in regulating the underlying pathophysiology of complex chronic conditions, such as obesity and diabetes (Cermakian & Boivin, 2009).

Circadian Misalignment (CRD) and Clinical Significance

Contemporary life, marked by widespread exposure to artificial light, irregular feeding schedules, and inadequate sleep, has led to a prevalent state of circadian disruption or “misalignment” between the body’s internal timing and external environmental cues (Schiavon et al., 2024). This circadian misalignment is intricately linked to an elevated risk of physiological dysfunction and systemic disease (Patel et al., 2022). The resulting deregulated rhythms can contribute to a wide array of negative health consequences,

including inflammation and chronic diseases such as Type 2 diabetes, obesity, and cardiovascular diseases (Patel et al., 2022; Schiavon et al., 2024).

The critical nature of this temporal control lies in the fact that CRs govern the fundamental energetic trade-off required for systemic homeostasis, specifically balancing energy storage against expenditure and maintaining redox integrity. When CRs fail to temporally separate necessary metabolic and redox functions, misalignment ensues, compromising basic cellular energetic efficiency. This breakdown in temporal partitioning provides a plausible mechanism by which circadian disruption acts as a primary, universal trigger for a spectrum of chronic metabolic and vascular diseases.

Chronosynchronization in Rehabilitation Science

The emerging field of clinical chronobiology underscores the therapeutic potential of targeting these temporal disorders (Tomatsu et al., 2025). Within the specific context of physiotherapy and rehabilitation science, the therapeutic re-synchronization of the circadian system represents a key clinical area that can be managed effectively through non-pharmacological interventions (Schiavon et al., 2024; Healy et al., 2021). A truly successful rehabilitative approach must aim for *Chronosynchronization*, which requires the simultaneous optimization of the three primary environmental time cues (*Zeitgebers*): exercise, nutrition, and sleep (Healy et al., 2021).

Molecular and Neural Architecture of the Circadian System

The Central Clock: Suprachiasmatic Nucleus (SCN)

The master regulatory pacemaker, which dictates systemic rhythmicity in mammals, is the Suprachiasmatic Nucleus (SCN), located in the hypothalamus of the brain (Cermakian & Boivin, 2009; Tomatsu et al., 2025). The SCN holds the critical responsibility for synchronizing all peripheral, tissue-specific clocks throughout the rest of the organism (Cermakian & Boivin, 2009; Tomatsu et al., 2025).

The primary mechanism that drives the SCN's entrainment (its alignment to the external 24-hour cycle) is photic signaling (Schiavon et al., 2024). Light is recognized as the most potent *Zeitgeber* (German for time giver) for the SCN clock system (Schiavon et al., 2024). Light signals are transmitted from the retina, adjusting the central clock to the external light-dark cycle, thereby initiating the synchronization cascade for peripheral clocks across the body (Cermakian & Boivin, 2009).

The Core Mechanism: Transcriptional-Translational Feedback Loop (TTFL)

At the fundamental cellular level, the self-sustaining nature of circadian rhythms is generated principally by the Transcriptional-Translational Feedback Loop (TTFL) (Tomatsu et al., 2025; Hastings et al., 2007).

The cycle is initiated during the Positive Phase when the key clock proteins CLOCK and BMAL1 form a heterodimer complex. This complex serves as the transcriptional activator for the core circadian genes, specifically *Per* (Period) and *Cry* (Cryptochrome) (Tomatsu et al., 2025).

The process continues into the Negative Feedback Phase. As the resulting PER and CRY proteins accumulate in the cytoplasm, they translocate back into the nucleus. Here, they exert an inhibitory effect, repressing the activity of the CLOCK/BMAL1 complex, thus completing the inhibitory feedback loop that generates the characteristic oscillation with a period of approximately 24 hours (Tomatsu et al., 2025).

Peripheral Clocks and Targeted Entrainment

Virtually every tissue and organ system, including the liver, adipose tissue, and skeletal muscle, possesses its own intrinsic peripheral clock mechanism, which is fundamentally driven by the TTFL (Cermakian & Boivin, 2009). While light is the dominant synchronizer for the SCN, peripheral clocks primarily respond to non-photic *Zeitgebers*. Among these, food availability and structured activity/rest cycles, particularly exercise, function as critical synchronizing cues (Schiavon et al., 2024).

From a physiotherapy perspective, skeletal muscle represents a critical peripheral oscillator target. Skeletal muscle responds robustly to physical activity, displaying significant changes in the expression of local clock components, such as *Per*, *Cry*, and *BMAL1* (Schiavon et al., 2024). This responsiveness indicates that physiotherapeutic interventions can focus on the dual goal of directly synchronizing these peripheral clocks. Empirical data demonstrates that the timing of exercise differentially impacts gene expression depending on whether the activity occurs at the beginning or the end of the active phase. This provides clear molecular evidence of the customized, powerful effect that physical activity timing exerts on local timekeeping.

The ability to manipulate exercise timing allows for localized chronosynchronization, distinct from the global, SCN-driven rhythm. Since exercise is a potent *Zeitgeber* for peripheral clocks like those in skeletal muscle, targeted *Chronexercise* enables clinicians to selectively optimize local tissue functions—such as performance, repair, and metabolism—even if the central clock’s synchrony is incomplete. This capability establishes timed exercise as a uniquely valuable translational tool, particularly in chronic conditions where muscle quality and metabolic flexibility are central therapeutic goals.

Circadian Regulation of Systematic Physiology in Rehabilitation

Rhythmic Control of Physical Performance and Musculoskeletal Function

A range of key physiological parameters relevant to rehabilitation, including physical exercise capacity, muscle strength, and endurance, exhibit distinct diurnal fluctuations

that are strictly governed by endogenous CRs (Schiavon et al., 2024).

Observations consistently indicate that peak muscle strength and overall physical performance generally occur during the afternoon and early evening hours (Schiavon et al., 2024). These natural performance peaks are linked to several sirkadiyen-controlled physiological factors, notably the daytime elevation of core body temperature and the optimization of underlying neuromuscular function (Schiavon et al., 2024).

At a molecular level, even the mitochondrial oxidative capacity, which is a critical determinant of endurance performance, follows a daily rhythm (Schiavon et al., 2024). This rhythmic profile leads to reports of strong time-of-day effects on measures of power and exercise capacity. These variations are partly correlated with the diurnal expression profiles of the gene (Schiavon et al., 2024).

Tendon Health and Rhythm Disruption

Tendon health is a high-priority area for physiotherapy due to the common occurrence of overuse injuries, or tendinopathies (Yeung, 2025). Tendons, being fibrous connective tissues composed primarily of Type I collagen, rely on stable biological timing. Available evidence demonstrates that a disrupted circadian rhythm negatively impacts the structural integrity and health of human tendons (Yeung, 2025). Consequently, understanding the mechanisms of circadian clock disruption in tendon tissue offers potential new strategies for informing the diagnosis and refining the therapeutic management of tendon injury and associated pain (Yeung, 2025).

Neuroendocrinology and Metabolic Homeostasis

The circadian system provides meticulous regulation over both hormonal secretion and overall metabolic flux (Cermakian & Boivin, 2009; Schiavon et al., 2024).

The secretion of Growth Hormone (GH) exhibits a pulsatile circadian pattern, characterized by pronounced nocturnal peaks. This timing is indispensable for anabolic processes and is crucial for efficient post-exercise recovery (Schiavon et al., 2024). Cortisol secretion is also rigorously directed by the central SCN pacemaker, following a distinct 24-hour pattern (Morris et al., 2022). Circulating cortisol concentrations reach their maximum concentration around the habitual sleep-to-wake transition and decline progressively toward the late night (Morris et al., 2022). Cortisol acts as the key catabolic signal that coordinates peripheral clocks, working synergistically with anabolic hormones (such as testosterone) to preserve anabolic-catabolic homeostasis (Morris et al., 2022).

The fact that the major peak of GH occurs nocturnally highlights that anabolic recovery is intrinsically tied to the nocturnal period, independent of when physical activity occurs during the day. Consequently, the success of muscle repair and protein synthesis

following exercise is directly dependent on the quality and timing of subsequent sleep. If a patient experiences circadian rhythm disruption (CRD) due to poor sleep hygiene, their critical peak anabolic signaling may be suppressed or phase-shifted, leading to chronically compromised recovery, persistent low-grade inflammation, and potential symptoms of overtraining. This mechanistic link emphasizes the necessity of prioritizing sleep management as a primary component of any effective rehabilitation protocol.

Metabolic Consequences and Exercise Timing

Disruption of the circadian clock at the molecular level significantly contributes to dysregulation of glucose and lipid metabolism (Cermakian & Boivin, 2009; Schiavon et al., 2024).

The molecular basis for this pathology is demonstrated by studies showing that the deletion of the gene in skeletal muscle results in diminished glucose uptake and reduced transporter levels (Schiavon et al., 2024). This evidence confirms the direct and significant role of the muscle clock in the pathogenesis of metabolic diseases, such as Type 2 diabetes.

Conversely, exercise serves as a potent positive regulator, enhancing the expression of and genes/proteins. This upregulation is believed to partially mediate the metabolic benefits of exercise, coinciding temporally with improvements observed in peripheral insulin sensitivity and maximal oxygen consumption (Schiavon et al., 2024).

These foundational physiological findings underscore the necessity of personalizing rehabilitation strategies based on the individual's specific chronotype and defined therapeutic objectives (Schiavon et al., 2024). When the goal is maximizing strength and power output, the afternoon timeframe is generally recommended due to performance peaks. However, if the primary goal is improving metabolic health in patients with conditions like Type 2 diabetes, early morning exercise may offer superior benefits. This is related to clock-driven fluctuations in carbohydrate metabolism, often correlating with lower perceived exertion and oxygen consumption during morning sessions (Schiavon et al., 2024).

This divergence highlights a crucial physiological trade-off that rehabilitation prescription must navigate: the choice between optimizing mechanical power output versus maximizing metabolic stress management. Afternoon timing intrinsically supports maximal physical output (force, velocity), while morning timing appears to optimize metabolic biomarkers (e.g., glucose clearance, lower perceived effort). The clinician must precisely define the therapeutic endpoint—be it performance enhancement or systemic metabolic health—before establishing the optimal *Zeitgeber* schedule.

Circadian Misalignment and Chronic Pain Pathophysiology

CRD as a Contributor to Central Sensitization

Circadian rhythm disorders (CRD) demonstrate a high degree of comorbidity in patients presenting with Chronic Musculoskeletal Pain (KKA) (Tüchler et al., 2022; Yeung, 2025). Significantly, disruption of the biological timing system is not merely coincidental but is actively implicated in the pathogenesis of KKA through the exacerbation of central sensitization (Tüchler et al., 2022). Central sensitization is a pathological state of neuronal hypersensitivity, which results in magnified pain perception (Tüchler et al., 2022).

Rhythmic Blood Pressure Anomalies and Vascular Stress

Patients suffering from KKA frequently exhibit anomalous circadian Blood Pressure (BP) profiles (Tüchler et al., 2022). These include the non-dipper pattern, where the physiological nocturnal drop in BP fails to occur, or the more severe inverse-dipper pattern, where nighttime BP rises above the daytime average (Tüchler et al., 2022).

This abnormal vascular pattern is hypothesized to initiate a mechanistic cascade that contributes directly to chronic pain :

1. **Oxidative Stress Generation:** Elevated or sustained nighttime BP generates excessive oxidative stress and localized tissue damage (Tüchler et al., 2022).
2. **Neuro-Inflammatory Cascade:** This stress, in turn, triggers inflammatory events and the activation of glial cells within the central nervous system (Tüchler et al., 2022).
3. **Enhanced Pain Perception:** The culmination of this process is an increased pain experience driven by persistent low-grade inflammation and amplified central sensitization (Tüchler et al., 2022).

This evidence establishes that CRD acts as a causal, mechanistic link that connects systemic vascular deregulation (abnormal BP) to the neuropathology underlying chronic pain (central sensitization). A critical clinical implication is that circadian dysregulation in KKA patients should not be regarded merely as a secondary symptom but rather as a causal mechanism (Tüchler et al., 2022). Therefore, therapeutic interventions must prioritize normalizing the patient's biorhythm through interventions like consistent sleep hygiene, regulated light exposure, and routine rhythmicity. Such interventions are inexpensive and simple to implement, yet they simultaneously address the central pain prognosis and mitigate the significant increased cardiovascular risk associated with the non-dipper BP pattern (Schiavon et al., 2024; Tüchler et al., 2022).

Circadian Gatekeeping of Pain Modulation

Pain perception is regulated temporally by the CR system, much like hormonal secretion and the sleep/wake cycle (Liang et al., 2021). The circadian rhythmicity observed in

pain is a complex output of oscillators distributed across the entire nociceptive pathway, including the Dorsal Root Ganglion (DRG), the spinal cord, and the descending pain modulatory system (Liang et al., 2021). These structures function as circadian “gatekeepers,” daily modulating the transmission and processing of nociceptive information (Liang et al., 2021).

The endogenous opioid system, which plays a central role in regulating pain and stress responses, exhibits circadian fluctuations in its activity (Liang et al., 2021). The finding that pain responses (e.g., those induced by morphine or naloxone injections) vary significantly across the 24-hour cycle implies an endogenous rhythm in the expression of opioid receptors or their downstream signaling components (Liang et al., 2021). This biological reality necessitates a chronopharmacological consideration for determining the optimal timing of all analgesic interventions, including non-pharmacological techniques such as manual therapy and electrotherapy applied within physiotherapy (Liang et al., 2021).

Strategic Chronotherapy in Physiotherapy and Rehabilitation

Chronotherapy is defined as the strategic timing of environmental *Zeitgebers* to correct circadian misalignment and maximize beneficial physiological responses, establishing it as a critical instrument in the rehabilitation sciences (Patel et al., 2022).

Chronexercise: Timing for Performance and Health Optimization

Physical exercise is classified as a powerful, non-photic *Zeitgeber* that exerts strong regulatory effects on the CR system (Schiavon et al., 2024). When implemented as programmed exercise, it specifically optimizes the local molecular clock within skeletal muscle, leading to beneficial adaptations in energy metabolism and mitochondrial biogenesis (Schiavon et al., 2024).

The optimal timing of the exercise session must be rigorously tailored to the specific expected physiological outcome :

- **Maximum Performance Target:** Given that muscle strength and physical capacity peak during the afternoon, this timeframe is recommended for high-intensity or power-focused training sessions to achieve the highest possible power output (Schiavon et al., 2024; Tüchler et al., 2022).
- **Metabolic Health Target:** For individuals with metabolic disorders, exercise performed in the early morning hours is suggested. This timing has been linked to lower perceived exertion and oxygen consumption, which may relate to clock-driven fluctuations in carbohydrate metabolism, suggesting that morning sessions are more appropriate for maximizing metabolic recovery (Schiavon et al., 2024).

Programmed exercise possesses the distinct capacity to synchronize peripheral molecular clocks, such as those found in skeletal muscle (Schiavon et al., 2024). For

example, studies involving running wheel activity showed that exercise performed at the beginning of the active phase had a more significant impact on reducing the amplitude of gene expression in the SCN compared to exercise performed late in the active phase (Schiavon et al., 2024).

Principles of Holistic Chronosynchronization and Personalized Chronotherapy (P-CT)

Physiotherapists occupy a key clinical position to utilize and manage environmental *Zeitgebers*—encompassing exercise, sleep, and light exposure—to restore normative patient biorhythms (Tüchler et al., 2022).

Sleep Hygiene and Lifestyle Management

Regulation of sleep patterns and adherence to rigorous sleep hygiene are considered the most fundamental and effective non-pharmacological methods for normalizing biorhythms (Tüchler et al., 2022). This basic intervention carries significant weight in both the prevention and long-term prognosis of chronic pain conditions (Tüchler et al., 2022).

Phototherapy and Environmental Control

The use of timed light exposure, often utilizing bright light lamps, is essential for correcting circadian phase shifts, which commonly arise from conditions like shift work or jet lag (Tomatsu et al., 2025; Tüchler et al., 2022). Conversely, maintaining dark environments during the night supports robust, normative melatonin secretion rhythms (Tüchler et al., 2022).

Individualized Programming

The assumption that a single “best time” exists for all training or rehabilitation outcomes is scientifically unsupported (Schiavon et al., 2024). Physical training recommendations must be strictly individualized based on a confluence of variables, including the patient’s intrinsic chronotype, genetic variants, specific health status, and dietary patterns (Schiavon et al., 2024). Aligning exercise sessions with a comprehensive chronotype assessment represents a compelling strategy to maximize the therapeutic metabolic and overall health benefits of physical activity (Schiavon et al., 2024).

The professional role of the physiotherapist necessarily expands beyond simply prescribing movement to actively managing the temporal environment of the patient. By strategically manipulating non-photic *Zeitgebers* (exercise) and managing photic *Zeitgebers* (light/dark schedules) and behavioral *Zeitgebers* (sleep hygiene), the clinician is executing clinical chronosynchronization. This integrated approach requires the clinician to possess a molecular understanding of how lifestyle factors impact

physiological timing, allowing them to use these elements as precision tools to optimize systemic function across performance, metabolism, and pain sensitivity.

Key Chronotherapeutic Interventions in Rehabilitation

The integration of chronobiological principles into practice involves applying specific interventions tailored to the mechanistic targets of the circadian system.

The Circadian Hierarchy and Molecular Targets

Understanding the therapeutic application of chronobiology requires knowledge of the core components of the circadian system and their primary entrainment signals.

The Suprachiasmatic Nucleus (SCN):

Functioning as the master pacemaker in the hypothalamus, the SCN maintains systemic rhythmicity for processes such as cortisol secretion and core temperature regulation. Its primary entrainment signal is Light (Photic Input), making its translational relevance the stabilization of global hormonal patterns and the regulation of the systemic sleep/wake cycle (Healy et al., 2021).

The Transcriptional-Translational Feedback Loop (TTFL):

This cellular mechanism, involving the core proteins CLOCK/BMAL1 and PER/CRY, is the endogenous generator of rhythm. It provides the fundamental basis for tissue responsiveness to temporal cues and influences specific gene expression.

Peripheral Clocks:

These clocks possess an intrinsic TTFL but are governed by local stimuli, primarily Activity/Exercise and Food Availability. They represent a direct therapeutic target for *Chronexercise* aimed at optimizing local performance and metabolic processes (Schiavon et al., 2024).

Strategic Chronotherapeutic Interventions

Specific *Zeitgeber* interventions are utilized to achieve distinct clinical objectives in rehabilitation:

- ***Regular Sleep/Wake Schedule:*** This intervention strongly synchronizes the SCN and stabilizes melatonin and cortisol profiles (Healy et al., 2021). The clinical objective is to mitigate central sensitization and inflammation, improve Chronic Musculoskeletal Pain (CCP) prognosis, and correct sleep disorders (Healy et al., 2021; Tüchler et al., 2022).
- ***Timed Exercise (Chronexercise):*** This method primarily entrains peripheral clocks, particularly in skeletal muscle (Schiavon et al., 2024). The clinical focus

is to maximize muscle performance and strength, optimize muscle metabolism, and reduce metabolic stress (Schiavon et al., 2024).

- **Bright Light Therapy:** Mechanistically, bright light induces SCN phase shifts and suppresses melatonin secretion. It is used to correct rhythm disorders (e.g., phase delay) and enhance wakefulness and alertness (Tomatsu et al., 2025; Tüchler et al., 2022).
- **Tendon Health Focused Timing:** This approach maintains the integrity and regulation of tendon collagen and extracellular matrix proteins. Its objective is to reduce the incidence of tendinopathy and accelerate tissue repair mechanisms (Yeung, 2025).

Conclusion

Clinical Potential of Circadian Integration

The comprehensive integration of circadian biology into clinical physiotherapy and rehabilitation practice, defined as Chronotherapy, introduces a powerful temporal dimension that enhances traditional treatment paradigms (Patel et al., 2022). Current evidence has refined the understanding of rhythm dysfunction, identifying it not merely as a frequent comorbidity but as a direct pathophysiological bridge connecting chronic pain states and systemic diseases (Tüchler et al., 2022). By expertly manipulating environmental *Zeitgebers*—specifically exercise, light exposure, and the sleep/wake cycle—physiotherapists gain the molecular leverage necessary to accelerate patient recovery processes and maximize targeted physiological responses (Patel et al., 2022; Schiavon et al., 2024).

Advanced Research Directions

While the translational momentum in chronobiology is substantial, further research is required to achieve high-fidelity clinical application in rehabilitation:

- **Development of Personalized Chronotherapy (P-CT):** Future research must prioritize the development of robust P-CT algorithms applicable to chronic pain, metabolic diseases, and obesity. The efficacy of treatment can be substantially enhanced by incorporating granular patient data, including individualized chronotype assessment and specific genetic variations (Schiavon et al., 2024). The current reliance on generalized population timing advice (e.g., “afternoon peak”) risks mistiming the intervention for individuals whose internal phase angle differs significantly from the external cycle. The development of accessible, reliable methods for chronotype and genetic profiling is therefore a crucial translational bottleneck that must be addressed to move chronotherapy into a true precision medicine framework.
- **Mechanistic Validation:** Subsequent studies need to precisely delineate the influence of rhythmic hormonal patterns (GH and cortisol) on the kinetics of post-exercise recovery (Schiavon et al., 2024).

- **Causality in Stress Pathways:** Deeper investigation into the explicit causal contribution of circadian misalignment to the generation of oxidative stress and the resulting chronic inflammatory status is warranted (Schiavon et al., 2024; Tüchler et al., 2022).
- **Translational Proof:** Establishing the exact molecular mechanisms by which physiotherapeutic interventions actively repair these identified pathophysiological bridges is necessary to solidify chronotherapy as an evidence-based and indispensable component of modern rehabilitation practice.

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