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REVIEW

CHRONOBIOTICS: CLASSIFICATIONS OF EXISTING CIRCADIAN CLOCK MODULATORS, FUTURE PERSPECTIVES

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The review summarizes recent achievements and future prospects in the use of chronobiotics for regulating circadian rhythms regulation. Special attention is paid to the mechanisms' action, their classification, and the impact of chemical interventions on the biological clock. Chronobiotics defined as a diverse group of compounds capable of restoring disrupted circadian functions, addressing challenges such as irregular work schedules, artificial light exposure or ageing. The review categorizes these compounds by their pharmacological effects, molecular targets, and chemical structures, underlining their ability to enhance or inhibit key circadian components like CLOCK, BMAL1, PER, and CRY. A particular focus is placed on the therapeutic applications of chronobiotics, including their potential for treating sleep disorders, metabolic issues, and age-related rhythm disturbances, underscoring their wide-ranging applicability in health care. Chronobiotic compounds have promising roles in maintaining physiological rhythms, supporting healthy aging, and enhancing personalised health care. Given their diverse therapeutic potential, chronobiotics are positioned as a significant avenue for further clinical application, marking them as a crucial area of ongoing research and innovation.

Key words: chronobiotics; circadian clock; circadian rhythms; classification; therapeutic perspectives, desynchronosis

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INTRODUCTION

Chronobiotics pharmacology is a burgeoning field of research investigating the influence of exogenous compounds on biological rhythms, specifically focusing on their ability to modulate the circadian clock. This area of study holds immense potential for addressing a wide range of health challenges, including sleep disorders, metabolic dysregulation, and mental health conditions. Understanding the mechanisms by which chronobiotics interact with the circadian system, we aim to develop novel therapeutic strategies for promoting optimal health and well-being. This review explores the current state of knowledge regarding chronobiotics, delving into their molecular mechanisms of action, therapeutic applications, and future research directions.

The circadian clock, a complex molecular machinery operating within cells, governs the cyclical fluctuations of various physiological processes, including sleep-wake cycles, hormone secretion, and metabolic activity. These rhythms are synchronised with the 24 h light-dark cycle, ensuring proper adaptation to the environment. Disruptions in circadian rhythms, often caused by factors such as shift work, jet lag, or exposure to artificial light, can have profound negative effects on health, increasing the risk of chronic diseases [1].

Chronobiotics, a diverse group of compounds that can influence the circadian clock, offer a promising avenue for restoring and regulating these rhythms, including age-related decline. Before classifying these compounds into distinct categories, it is important to first describe the circadian system.

1. CORE CIRCADIAN CLOCK

The intricate progress of life, with its rhythmic ebb and flow, is orchestrated by a remarkable internal timekeeper: the circadian clock. This endogenous system, present in nearly every living organism, governs the cyclical fluctuations of various physiological processes, ensuring harmony between our internal biology and the external environment. In mammals, the circadian clock is a complex molecular network, residing within cells and driven by a finely tuned interplay of genes and proteins [2]. This review delves into the core architecture of this cellular timekeeper, exploring the key components and their intricate interactions that underpin the rhythmic precision of mammalian life (Fig. 1).

The foundation of the mammalian circadian clock lies within a self-sustaining transcriptional-translational feedback loop, involving a core set of clock genes and their protein products. This intricate network, housed within the suprachiasmatic nucleus (SCN) of the hypothalamus, acts as the central pacemaker, coordinating rhythmic activity throughout the body. Two key transcription factors reside at the heart of this molecular machinery, CLOCK (backronym for *circadian locomotor output cycles kaput*) and BMAL1 (*Basic helix-loop-helix ARNT-like protein 1* or

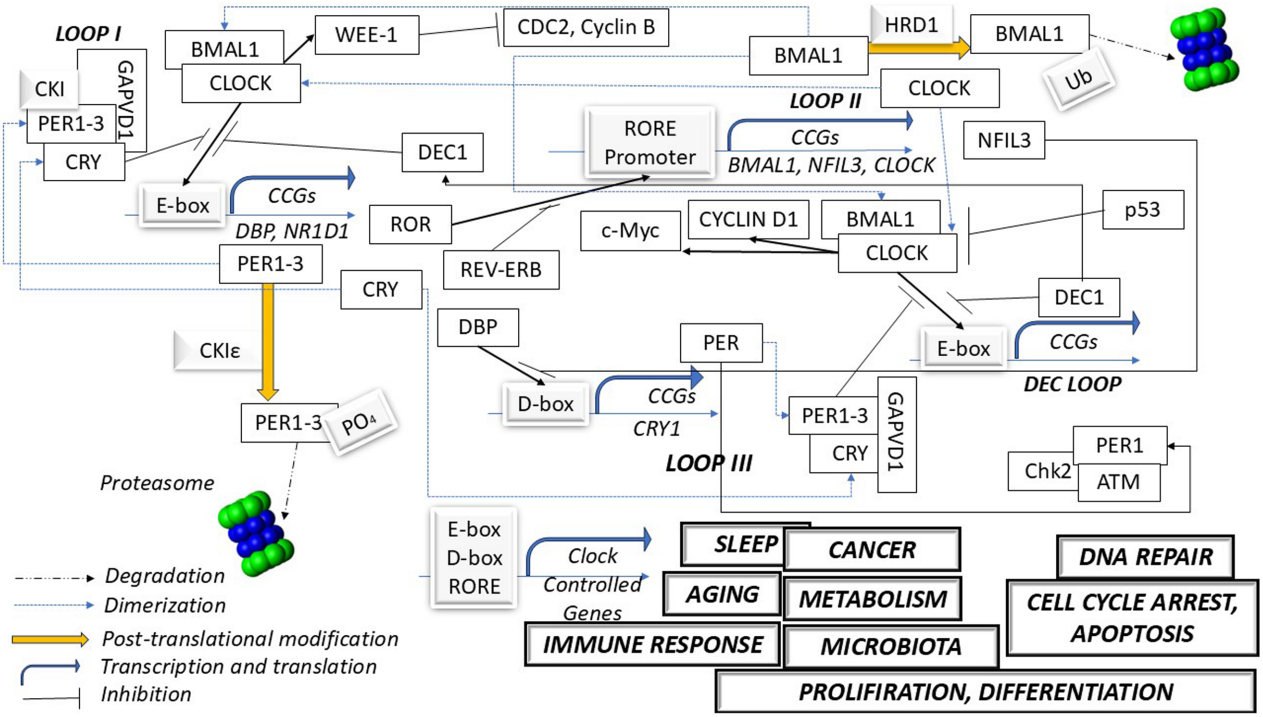

Figure 1. The molecular circadian clock of mammals.

aryl hydrocarbon receptor nuclear translocator-like protein 1 (ARNTL), or *brain and muscle ARNT-like 1*). This binding event initiates the transcription of downstream clock genes, namely *Period* (*Per*) and *Cryptochrome* (*Cry*) [3].

The PER and CRY proteins, once translated, form complexes that are translocated back to the nucleus, where they inhibit the activity of the CLOCK/BMAL1 complex. This negative feedback loop, through a series of intricate protein interactions, regulates the cyclical expression of the clock genes, ultimately generating a 24-hour rhythm.

Beyond this core loop, other feedback mechanisms contribute to the robustness and precision of the circadian clock. One such loop involves the nuclear receptor, REV-ERBα (*protein product of gene Nr1d1*), which binds to RORE elements in the BMAL1 promoter, suppressing its transcription. Another layer of regulation is provided by the positive feedback loop involving RORα (*RAR-related orphan receptor alpha*), which activates BMAL1 transcription. An intricate interplay of these molecular components, coupled with post-translational modifications like phosphorylation and ubiquitination, ensures a precise and robust circadian rhythm [4].

This review lays the groundwork for understanding the molecular bases of the circadian clock, setting the stage for exploring the impact of pharmacological interventions on its function. The following chapters consider into the external chemical regulation of the circadian clock, its role in diverse pathogenesis, and the potential therapeutic applications of chronobiotics in modulating its function.

2. CLASSIFICATIONS OF CHRONOBIOTICS

Chronobiotics can be classified in various ways, depending on their structure, function, and pharmacological targets (Fig. 2)

Functional classification is based on effects and needs frequent revisiting; the chronobiotics may be modulators of circadian rhythms or chronotoxicants (disrupting it in cancer cells). Chronobiotics may rescue circadian oscillations protecting from desynchronosis or just modify the period or induce phase shift of the oscillations. The highest interest is stimulated in the scientific community by the search of harmonising chronobiotic agents, which rescue circadian rhythms in elderly.

An additional, optional category, and the most varied one, is the source-based class within the repurposed chronobiotic system. This functional classification is especially relevant when the clock-associated target of certain medications is unknown. Such categorization could be valuable for clinicians, as it includes drugs like antibiotics, certain immunosuppressants, disinfectants, fungicides, and anesthetics, which may modulate circadian rhythms due to their off-target activity or adverse effects on the circadian clock [5].

Chronobiotics can be classified in several ways based on their pharmacological class, molecular targets, chemical structure, and functional effects. Understanding these classifications helps to categorize the diverse range of agents that can be used to modulate circadian rhythms, depending on their therapeutic use or biological mechanism of action.

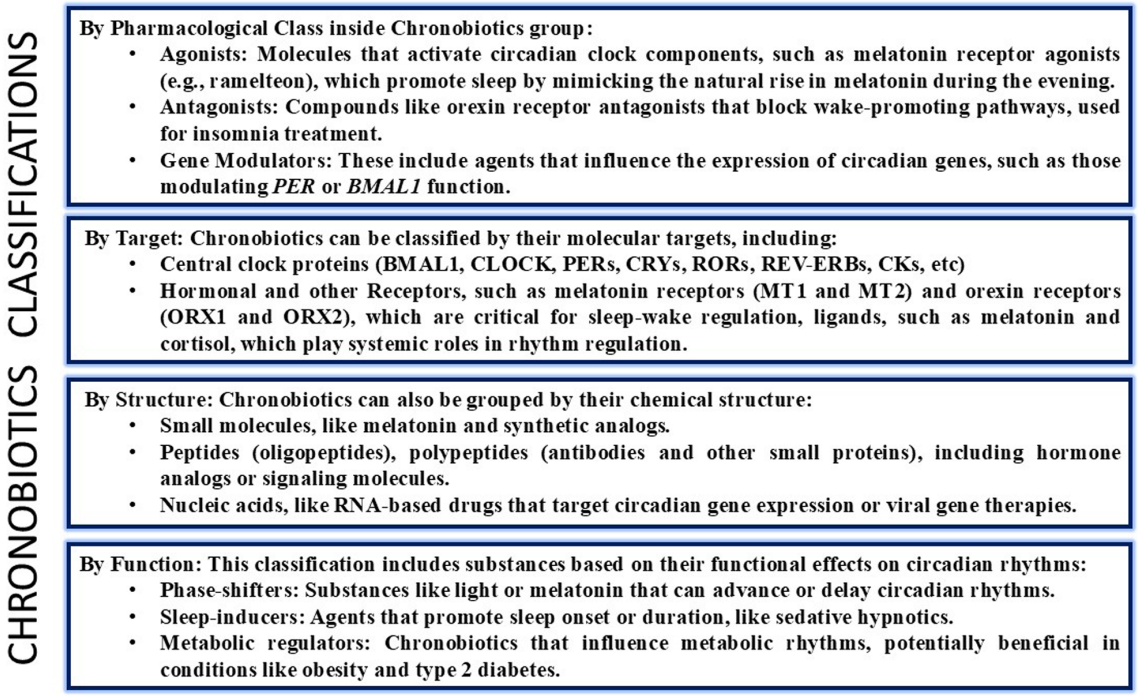

Figure 2. Classifications of chronobiotics.

2.1. Classification by Pharmacological Class

Chronobiotics can be grouped based on how they pharmacologically interact with the circadian system. These agents can be categorized based on their pharmacological interactions with the circadian clock, specifically as agonists, antagonists, or gene modulators.

2.1.1. Agonists

Agonists are compounds that activate the circadian clock by enhancing the function of core clock proteins. For example, melatonin receptor agonists like ramelteon bind to melatonin receptors (MT1, MT2), mimicking the natural rise in melatonin during the evening and promoting sleep [6]. Another example is several small molecules acting as agonists for cryptochrome (CRY), a key component in the circadian rhythm regulation. Notable examples include KL001 and other compounds which have shown potential in extending lifespan and improving circadian rhythms in model organisms [7].

2.1.2. Antagonists

These compounds block the activity of wake-promoting pathways. A key example orexin receptor antagonists such as suvorexan, which inhibit orexin signalling (important for wakefulness) and are used in the treatment of insomnia by promoting sleep onset and maintenance [8]. Dual orexin receptor antagonists (DORAs), such as DORA-22, work by blocking the arousal-promoting activity of orexin peptides, helping to induce sleep without altering normal sleep architecture [9].

2.1.3. Gene Modulators

This class includes agents that affect circadian gene expression. These substances modulate core clock proteins such as PER (Period) or BMAL1, which play major roles in regulating circadian rhythms. For example, CK1δ inhibitors prevent degradation of PER proteins, thereby influencing the length of the circadian period [10]. These modulators can include various agents, such as microRNAs. miR-25-3p has been identified as a new regulator of the *Per2* gene, capable of suppressing its expression through post-transcriptional modifications [11].

2.2. Classification by Target

Chronobiotics can also be categorised by their molecular targets, particularly focusing on key elements of the circadian clock and their related pathways.

2.2.1 Central Clock Proteins as Targets

These proteins form the core mechanism of the circadian clock, including PER, CRY, BMAL1, and CLOCK. Chronobiotics that target these proteins directly affect the key processes that regulate circadian rhythm are described in the following paragraph. PF-670462 is a selective inhibitor of casein kinase 1 epsilon (CK1ε) and delta (CK1δ), primarily targeting degradation of Period (PER) proteins, which are essential for maintaining circadian rhythms. By inhibiting CK1δ, PF-670462 promotes the nuclear retention of PER2, thereby extending the circadian period [10, 12].

2.2.2. Hormonal and Other Receptors

Important receptors involved in circadian rhythm regulation include melatonin receptors (MT1 and MT2) and orexin receptors (ORX1 and ORX2). Chronobiotics like melatonin or orexin antagonists directly interact with these receptors to regulate sleep-wake cycles and other circadian-controlled processes.

One of the key hormones involved is melatonin, produced by the pineal gland. Melatonin levels rise at night and fall during the day, helping to regulate the sleep-wake cycle. It also influences metabolic processes, and disruptions in melatonin rhythms have been linked to conditions such as obesity and insulin resistance [13, 14]. Another important hormone is cortisol, commonly known as the stress hormone. Cortisol follows a clear circadian rhythm, peaking in the early morning and gradually declining throughout the day. It is essential for regulating metabolism and immune responses, and disturbances in cortisol rhythms can lead to health issues like metabolic syndrome [15, 16].

2.3. Classification by Structure

Chronobiotics can also be grouped by their chemical structure, which affects how they are absorbed, distributed, and metabolised in the body.

2.3.1. Small Molecules

Small molecules are low molecular weight compounds that can modulate biological processes, including circadian rhythms. As *in silico* design of drugs developing, the use of small molecules as chronobiotics is expanding. For instance, KL001 and KS15 have been investigated for their potential to extend lifespan and alter circadian rhythms in model organisms like *Drosophila melanogaster* [17]. Another small molecule, nobiletin, has shown promise in enhancing circadian rhythms while offering protective effects against metabolic syndrome, further underscoring the therapeutic potential of small molecules in circadian regulation [18].

2.3.2. Peptides and Polypeptides, Nucleic Acids

RNA-based drugs can directly influence transcription of circadian genes, which are crucial for maintaining the body's internal clock. These drugs can modulate the expression levels of critical regulatory proteins and RNA-binding proteins (RBPs) that influence the stability and translation of circadian mRNAs. For example, studies have demonstrated that RBPs such as Cirbp and Rbm3 are pivotal in regulating the amplitude of circadian gene expression through processes like alternative polyadenylation (APA) [19, 20]. This regulation allows fine-tuning of the circadian rhythms, offering potential therapeutic strategies for circadian-related disorders.

2.4. Classification by Function

Chronobiotics can be also classified by their functional role, focusing on the specific physiological effects they effect on the circadian system.

2.4.1. Phase-Shifters

These substances are used to change circadian rhythm helping to reset the internal clock. Phase-shifters primarily work by affecting the circadian clock through various mechanisms. Melatonin is one of the most recognised chronobiotics known for its ability to shift the phase of circadian rhythm. It is especially useful in resetting sleep-wake cycles [21, 22].

2.4.2. Sleep-Inducers

These agents promote sleep onset or increase sleep duration, playing a critical role in the treatment of insomnia and other sleep disorders. Sedative hypnotics such as benzodiazepines and non-benzodiazepine hypnotics fall into this category, sleep-wake cycles helping regulation by depressing central nervous system activity [23, 24].

2.4.3. Metabolic Modulators

Some chronobiotics influence metabolic rhythms, which are closely tied to circadian regulation. Agents of this category may help treat metabolic conditions such as obesity or type 2 diabetes by modulating circadian-controlled metabolic pathways. For instance, REV-ERBα plays a crucial role in the circadian clock, helping to regulate daily metabolic rhythms. It ensures that metabolic processes are aligned with the body's internal clock, optimising energy use during periods of activity and rest. When these rhythms are disrupted, it can lead to metabolic imbalances and related health issues [25].

In the next chapter, we pay attention to the core clock which elements are known to be key targets for precise modulation by chronobiotics.

3. KEY MOLECULAR TARGETS OF CHRONOBIOTICS

The present review divides the core clock on four main loops which are responsible for functioning of the circadian system of the organism; each of the loop is associated with its own small molecules and macromolecules, which may be considered as chronobiotics.

3.1. Positive Loop CLOCK(NPAS2)/BMAL1(ARNTL)

Understanding the molecular mechanisms governing the circadian clock has opened avenues for developing targeted pharmacological interventions. These modulators can be broadly categorized into CLOCK and NPAS2 activators aimed to enhance the activity of CLOCK and NPAS2, potentially promoting the transcription of clock-controlled genes and restoring disrupted circadian rhythms. Some potential examples include synthetic ligands, binding to CLOCK or NPAS2, promoting their activation and enhancing their transcriptional activity [26]. Small-molecule inhibitors inhibit the activity of PER and CRY, thereby increasing the availability of free CLOCK/BMAL1 complexes and promoting downstream genes transcription [27]. BMAL1/ARNTL activators offer a promising approach to restoring circadian rhythmicity. These could include small-molecule agonists directly activating *BMAL1* expression, enhancing its transcriptional activity

and promoting the expression of clock-controlled genes like 1A-116 or pterostilben (the ligand of ROR inducing the transcription of *BMAL1*) [28, 29].

Gene therapy strategies is an approach aiming at the increase in BMAL1/ARNTL expression by introducing exogenous *BMAL1*/*ARNTL* genes into target cells [30]. Conversely, CLOCK and NPAS2 inhibitors decreasing CLOCK or NPAS2 activity may be beneficial in certain contexts, particularly in diseases characterized by excessive CLOCK/BMAL1 activity is implicated. Small-molecule antagonists like CLK8 directly bind to CLOCK thus preventing their activation and reducing their transcriptional activity [30].

The development of pharmacological modulators targeting the core clock proteins holds significant promise for treating various diseases. However, several challenges remain to be solved. This includes demonstration that the specific targeting of CLOCK, NPAS2, or BMAL1/ARNTL is crucial to minimise off-target effects on other signalling pathways. The CLOCK/BMAL1 dimer has a wide range of target promoters inducing side effects and it still remains unclear how to increase binding specificity. Developing compounds that can effectively reach the target tissues and maintain their efficacy for extended periods remains a significant challenge. The complex nature of the circadian clock and its diverse functions requires rigorous clinical trials to assess the safety and efficacy of these future and existing modulators.

Despite these challenges, the therapeutic potential of modulating core clock proteins is undeniable. Ongoing research efforts are focused on developing novel, safe, and effective pharmacological agents, paving the way for the development of personalised therapies for a wide range of diseases linked to circadian dysregulation.

3.2. Negative Loop PER/CRY

3.2.1. The Molecular Framework of Period/Cryptochrome Complex

The Per proteins (including Per1, Per2, and Per3) and Cry proteins (including Cry1 and Cry2) are integral components of the circadian feedback loop. The Per and Cry proteins are synthesized in response to CLOCK/BMAL1 activity, which is the driving force behind the transcription of *Per* and *Cry* genes [31, 32]. Once synthesized, the PER and CRY proteins oligomerize and translocate to the nucleus, where they inhibit the CLOCK/BMAL1 activity, thereby closing the feedback loop. The rhythmic expression of these proteins ensures that the cellular activities oscillate in accordance with the external light-dark cycle, which is crucial for synchronizing physiological processes. Given their central role in circadian regulation, Per and Cry proteins represent promising targets for pharmacological intervention to restore circadian balance and address associated disorders [33].

3.2.2. Pharmacological Modulators of Period Proteins

Pharmacological modulators targeting Per proteins can be broadly categorized into activators and inhibitors, each playing a distinct role in the modulation of circadian rhythms.

3.2.3. Activators of Period Proteins

Certain small molecules have been identified that enhance the expression and stability of Per proteins. For instance, compounds such as SR9009 and its analogs activate the Rev-Erb pathway, leading to increased transcription of Per genes. By enhancing Per expression, these compounds can potentially resynchronize disrupted circadian rhythms and may be beneficial in conditions characterized by circadian dysregulation [34–36].

The use of gene therapy to boost *Per* expression through viral vector-mediated delivery additionally holds promise. This strategy could restore normal Per function in tissues where circadian rhythms are disrupted, paving the way for innovative treatment options. The overexpression approach demonstrates life extension in the model organism *Drosophila melanogaster* [37].

3.2.4. Inhibitors of Period Proteins

In contrast, certain conditions may necessitate the inhibition of Per proteins. This approach can be advantageous in cases where excessive Per activity contributes to pathology, such as in certain psychiatric disorders or tumorigenesis [38].

Small-molecule antagonists selectively inhibiting PER protein function have not been identified yet, thereby enhancing the activity of the CLOCK/BMAL1 complex. For instance, small-molecule compounds capable of disrupting the PER-CRY complex may enhance the transcriptional activity of the CLOCK/BMAL1 heterodimer, thus promoting the expression of downstream targets affected by circadian disruption [39].

3.2.5. Artificial Protein Modulators as Chronobiotics

The key clock protein PER is undergoing phosphorylation naturally. One of the promising approaches to tackle this issue artificially is taken from gerontological studies of α-synuclein, precisely from papers on hydrolyzing hyperphosphorylated α-synuclein [40]. The intervention to posttranslational modifications of PER may stabilise this repressive element and improve the robustness. The effects of compounds of this group remain unknown in chronobiology, except the LH846 [41].

3.3. Pharmacological Modulators of Cryptochrome Proteins

Similar to the Per proteins, Cry proteins serve as vital regulators of the circadian clock, and their modulation has gained attention in pharmacological research.

3.3.1. Activators of Cryptochrome Proteins

Activating Cry proteins can provide a mechanism to reinforce the negative feedback on the CLOCK/BMAL1 activity, thereby strengthening circadian regulation. Several natural compounds have been found to enhance Cry activity or physically activate it like KL001 [42].

For example, resveratrol, a polyphenol found in red wine, has been demonstrated to upregulate Cry expression, potentially offering therapeutic benefits in disorders arising from circadian imbalance [43]. The development of synthetic small-molecule agonists that target Cry proteins is an area of active research. Such compounds could increase the stability of Cry proteins, prolonging their repressive effects on CLOCK activity and ultimately leading to better circadian synchronization [43].

3.3.2. Inhibitors of Cryptochrome Proteins

While enhancing Cry function is beneficial in many contexts, inhibitors of Cry activity have their therapeutic rationale, especially in specific disease states. Research efforts have yielded small-molecule inhibitors like KS15 and SR8278 capable of disrupting Cry function and facilitating CLOCK/BMAL1 activity [44].

For instance, compounds that disrupt the interaction between CRY and PER could lead to reactivation of the CLOCK/BMAL1 complex, serving as a potential treatment strategy in circadian-related disorders where excessive repression is problematic [45]. The class of CRY ligands is the biggest among chronobiotics; it includes over 150 compounds, which are majorly derivatives of KL001 and KS15.

In plants, small proteins known as BIC1 and BIC2 inhibit cryptochrome functions by preventing dimerization in response to light. This inhibition alters critical traits such as plant growth and flowering. The BIC proteins establish a feedback mechanism that down-regulates CRY activity under continuous light conditions, indicating their role in adapting plant responses to environmental changes. Possibly this natural CRY inhibition mechanism will help to boost discovery of novel polypeptide drugs [46, 47].

3.4. Future Perspectives of PER/CRY Targeting

Novel data include the NRON (CSNK1E, GSK3B, and DYRK1A) complex in the list of potential targets affecting PER/CRY nuclear translocation successfully. This discovery opens the alternative pathway for PER/CRY dimer activity control, the chronobiotics effects of genetic targeting of the complex are documented, but the pharmacological interventions are not [33].

3.5. The REV-ERB/ROR Stabilizing Loop

An additional stabilisation loop involving the nuclear receptors REV-ERBs and RORs fine-tunes this core oscillator.

REV-ERBs (α and β) act as transcriptional repressors, binding to ROR response elements (ROREs) to inhibit Bmal1 expression. RORs (α, β, and γ) are transcriptional activators that compete with REV-ERBs for RORE binding, promoting *Bmal1* transcription. This REV-ERB/ROR mechanism stabilizes the core clock and regulates many clock-controlled genes. Pharmacological targeting of REV-ERBs and RORs is developed enough. Several small molecules have been developed to modulate REV-ERB and ROR activity: REV-ERB agonists like SR9009 and SR9011 can lengthen the circadian period and have therapeutic potential for metabolic disorders [48].

ROR agonists like nobiletin and CGP52608 enhance circadian rhythms and protect against metabolic syndrome in mice. ROR inverse agonists like SR3335 and T0901317 can disrupt circadian rhythms [48].

By targeting the RORE-stabilization loop, these small molecules can robustly modulate circadian rhythms and physiology. KK-S6 acts via the RORE-dependent mechanism by reinforcing the REV-ERBα activity [49]. Further research is needed to develop clinically useful chronotherapeutics.

3.6. DEC1-Stabilising Loop

DEC1, a crucial component of the circadian clock system; it functions as a transcriptional repressor, modulating the activity of CLOCK and BMAL1. The DEC1's primary mechanism involves binding to E-boxes in target gene promoters, inhibiting CLOCK/BMAL1-mediated transcription, which is essential for maintaining the proper timing and phase of circadian rhythms. Studies demonstrate that DEC1 overexpression delays the phase of clock genes while its deficiency advances their phase, thus demonstrating its critical role in the circadian clock fine-tuning [50].

DEC1, a basic helix-loop-helix transcription factor, is a novel target gene of the p53 tumor suppressor and a mediator of p53-dependent premature senescence. DEC1 is induced by the p53 family and DNA damage in a p53-dependent manner [50]. p53 proteins bind to and activate the *DEC1* gene promoter. Overexpression of DEC1 induces G1 arrest and promotes senescence. Targeting endogenous DEC1 attenuates p53-mediated premature senescence. DEC1 overexpression induces senescence in p53-knockdown cells, albeit to a lesser extent. DEC1-induced senescence is p21-independent. These findings establish DEC1 as a key effector downstream of p53 in promoting premature senescence; they provide a deeper understanding of the molecular mechanisms underlying tumour suppression through cellular senescence [50].

While DEC1-oriented chronobiotics remain elusive, the potential therapeutic implications of modulating DEC1 expression have spurred interest in developing compounds that target this crucial

circadian regulator, opening avenues for novel treatments for various pathologies, including pulmonary fibrosis and related conditions.

4. HORMONES AS SYSTEMIC MODULATORS OF PHYSIOLOGICAL CIRCADIAN CLOCK

Melatonin is a key regulator of circadian rhythms, with its levels rising in the evening and falling in the morning. Melatonin acts on two main receptor subtypes, MT1 and MT2, which are involved in different aspects of sleep regulation [51]. MT1 receptors are primarily responsible for circadian rhythm entrainment and appear to be the main target for melatonin's effects on sleep onset. MT2 receptors modulate REM sleep and have been implicated in the regulation of anxiety and mood. Melatonin receptor agonists like ramelteon and agomelatine can be used to treat insomnia by promoting sleep onset [52]. However, selective MT1 or MT2 agonists may be more effective than non-selective agents for targeting specific sleep disorders [52].

The orexin/hypocretin system is a key regulator of arousal and wakefulness. Orexin acts on two G protein-coupled receptors, OX1R and OX2R, which are involved in different aspects of sleep-wake regulation: OX2R is the primary receptor mediating the arousal effects of orexin and promoting wakefulness [53]. OX1R also contributes to arousal but appears to play a more modulatory role. Dual orexin receptor antagonists (DORAs) like suvorexant and lemborexant are a new class of sleep medications that promote sleep by blocking both OX1R and OX2R. These agents have shown efficacy in treating insomnia with a favourable safety profile [53].

4.1. Steroids and Circadian Rhythms

Progesterone, DHEA (dehydroepiandrosterone), cyproterone, and drospirenone are neurosteroids that may influence circadian rhythms and sleep-wake cycles, but their exact mechanisms are not fully elucidated. Progesterone has been shown to interact with GABA receptors and may promote sleep [54]. DHEA has complex effects on mood, cognition, and sleep, likely mediated through multiple receptor systems. Cyproterone is a progestogen with anti-androgenic properties used to treat conditions like hirsutism and acne [55]. More research is needed to clarify the specific roles of these neurosteroids in regulating sleep and circadian rhythms. Their effects likely involve complex interactions with neurotransmitter systems and other neuromodulators like melatonin and orexin. In summary, melatonin, orexin, and neurosteroids are important regulators of circadian rhythms and sleep-wake cycles, with therapeutic implications for treating insomnia and other sleep disorders. Selective targeting of melatonin and orexin receptors may provide more effective and specific treatment options in the future [54, 55].

5. MACROMOLECULAR CHRONOBIOTICS AND CHRONOBIOTIC SUBSTANCES (BIOPREPARATIONS)

The term macromolecular chronobiotics collects a large group of bioorganic molecules, such as proteins, nucleic acids, and complex compounds, that can modulate or influence circadian rhythms of the body.

Antibodies can bind directly to circadian proteins such as Period (PER), Cryptochrome (CRY), CLOCK, and BMAL1, inhibiting their function. For example, an antibody targeting PER proteins can prevent their accumulation in the nucleus or their interaction with other clock components, disrupting the negative feedback loop essential for the circadian rhythm [55]. Reischl et al. have demonstrated that β-TrCP1-mediated degradation of PER2 is essential for circadian dynamics, suggesting that interfering with this process could modulate circadian rhythms [56].

Another mechanism involves the modulation of protein stability. The stability and degradation of clock proteins are critical for the timing of the circadian clock [57]. Antibodies can influence the stability of these proteins by interfering with their degradation pathways. For instance, antibodies against the E3 ubiquitin ligase β-TrCP, which targets PER and CRY proteins for degradation, can stabilize these proteins, leading to changes in the circadian period [57, 58]. By stabilising PER proteins, antibodies can lengthen the circadian period, potentially correcting disorders characterized by a shortened circadian cycle.

In addressing the challenge of reliably assessing circadian clock proteins due to the scarcity of specific and validated antibodies, researchers undertook the generation and characterization of antibodies against key circadian proteins: PER1, PER2, BMAL1, and CLOCK. Using mice and hamsters as model organisms, le Sauter et al. focused on the suprachiasmatic nucleus (SCN), the brain region responsible for generating daily rhythms in behaviour and physiology [59]. By examining protein expression at peak and trough times and employing mice with targeted disruptions of the relevant genes, they confirmed the specificity and effectiveness of the antibodies. Their efforts resulted in identification of antibodies that reliably labelled these clock proteins in the SCN using immunocytochemistry. Antibodies as inhibitors represent a novel and promising class of macromolecular chronobiotics with the potential to modulate circadian rhythms at a molecular level.

5.1. RNA and AS-Oligonucleotides Against Circadian Genes

RNA therapeutics represent a transformative approach in modern medicine, utilizing ribonucleic acid (RNA) molecules to treat a variety of diseases. This innovative field encompasses several types

of RNA-based treatments, including messenger RNA (mRNA), small interfering RNA (siRNA), and antisense oligonucleotides (ASOs), each designed to manipulate gene expression and protein synthesis within cells [60].

Targeted disruption of miRNA-128a expression specifically within the cartilage results in the normalization of circadian clock gene expression and a significant reduction in the severity of osteoarthritis [61]. Angelman syndrome (AS), a severe neurodevelopmental disorder, is characterized by intellectual disability, developmental delay, seizures, and characteristic behavioural features [62]. The syndrome arises from a loss-of-function mutation in the maternal allele of the *UBE3A* gene, which encodes the ubiquitin protein ligase E3A. While paternal *UBE3A* is typically silenced in neurons by the antisense transcript UBE3A-ATS, a promising therapeutic avenue for AS involves reactivating the paternal allele by suppressing UBE3A-ATS. Previous studies have suggested a narrow therapeutic window for such interventions, with the greatest benefit observed when *UBE3A* expression is restored in early development, interventions may harmonize circadian activity of mice with the syndrome [63].

In recent research, it has been demonstrated that microRNAs play significant roles in the regulation of the circadian clock, particularly in *Drosophila* but also in a few studies on humans and other small animals. The control of clock-regulated gene expression will be the focus of the field, as our current understanding of the role that miRNAs play in clock regulation is limited [64, 65].

5.2. Probiotics

Recently, there has been a rising interest in probiotics because of their potential antioxidant and anti-inflammatory effects. There is emerging evidence [66] that gut microbiota play a role in regulating circadian rhythms, and probiotics have been explored as potential chronobiotics due to their ability to modulate gut-brain interactions. Specific strains of probiotics may influence the body's internal clock by interacting with the circadian regulation of metabolism, immune function, and even mood. For example, certain *Lactobacillus* and *Bifidobacterium* strains can impact circadian gene expression in peripheral organs like the liver and intestines, indirectly influencing the central circadian clock in the brain [67].

Probiotics could be beneficial in addressing circadian disruptions caused by things like shift work, or chronic stress [68, 69]. By helping to stabilize circadian rhythms, they may also support overall metabolic and immune health [70, 71]. These helpful bacteria have the potential to act as a new type of macromolecular chronobiotics by regulating the gut microbiome and, in turn, interacting with the body's internal clock system.

5.3. Prebiotics

Recent research has shown that prebiotics can alter the composition of the gut microbiota, leading to significant changes in circadian behaviour. In one study [72], Sprague Dawley rats fed a prebiotic diet exhibited a greater capacity to realign their sleep and core body temperature rhythms after experiencing chronic disruption of their circadian cycles. This was associated with an increased abundance of beneficial gut bacteria, such as *Ruminiclostridium* 5 and *Parabacteroides distasonis*. These changes in gut microbiota composition were linked to improved sleep quality and the restoration of core circadian functions. In another study, researchers investigated the effects of prebiotics on non-alcoholic fatty liver disease, Wistar albino rats were fed a high-fructose diet combined with a prebiotic supplement containing grape seed extract. Results showed that prebiotics significantly reduced glucose and ALT levels, improved liver structure by reducing adiposity, and enhanced the expression of circadian clock genes like *Bmal1* and *Clock* [73]. Overall, prebiotics represent a promising class of chronobiotic agents capable of restoring circadian rhythm through their effects on the gut microbiota and related metabolic pathways. All of this research in the prebiotics area may become an integral part of dietary strategies aimed at promoting better health through circadian regulation.

6. CHRONOBIOTICS AS POTENTIAL GEROPROTECTORS

Chronobiotics, such as melatonin and its synthetic analogs, show promise in geroprotection by restoring circadian rhythms that become disrupted with age. Age-related circadian changes, like reduced amplitude of rhythms, phase shifts, and dysregulated gene expression, contribute to physiological decline, including sleep disturbances, metabolic disorders, and cognitive impairment [7, 74–76]. Melatonin supplementation improves sleep patterns, resynchronises disrupted circadian rhythms, and offers neuroprotective and antioxidant benefits [77–79]. Additionally, compounds like REV-ERBα agonists and NAD+ precursors target circadian-controlled metabolic pathways, enhancing insulin sensitivity, reducing inflammation, and promoting healthy ageing [35, 80–84]. Chronobiotics may also support immune function by regulating inflammation and bolstering the body's defence against age-related diseases [85, 86].

CONCLUSIONS

The concepts of chronobiotics classification were fragmentary mentioned in different reviews, noteworthy the present paper was an attempt to unite them all to improve the navigation in the field. The narrow and not properly studied field of chronobiotics holds

immense promise for addressing a vast range of medical challenges linked to circadian disruption. This review has highlighted the significant progress made in understanding the molecular mechanisms underlying circadian rhythmicity and the therapeutic potential of chronobiotic interventions associated with numerous targets of different origin. Notably, the development of novel chronobiotics and classes of these drugs, targeting specific pathways within the circadian clock and in the closest proximity, offers a targeted approach to restore disrupted rhythms and alleviate associated health conditions. However, a greater emphasis on robust preclinical and clinical studies is essential to translate this promise into tangible therapeutic benefits, over 70 FDA-approved drugs have been repurposed as chronobiotics [5].

Future research should prioritize the development of personalized chronobiotic therapies (including temporally organized chronotherapies), accounting for individual variations in chronotype and sensitivity to specific interventions. Moreover, the long-term safety and efficacy of chronobiotics need to be carefully evaluated, ensuring that these promising therapeutic agents can be safely and effectively integrated into clinical practice and entering novel recommendations. Ultimately, the integration of chronobiotic strategies into a broader holistic approach to health management, healthy ageing encompassing lifestyle adjustments, behavioural interventions, and tailored pharmacological therapies, holds the key to harnessing the full potential of chronobiotics in optimising human health and well-being.

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COMPLIANCE WITH ETHICAL STANDARDS

This article does not contain any research involving humans or the use of animals as objects.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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ХРОНОБИОТИКИ: КЛАССИФИКАЦИИ СУЩЕСТВУЮЩИХ МОДУЛЯТОРОВ ЦИРКАДНЫХ РИТМОВ, ПЕРСПЕКТИВЫ НА БУДУЩЕЕ

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В обзоре рассматриваются последние достижения фармакологии в контексте перспективы использования хронобиотиков для контроля циркадных ритмов с учётом механизмов действия, классификации и влияния на биологические часы клетки. Хронобиотики выделяются как разнородная группа соединений, способных восстанавливать циркадные ритмы, нарушенные, например, в результате посменной работы или воздействия искусственного света, либо старения организма. В обзоре приведены классификации хронобиотиков по их фармакологическим эффектам, молекулярным мишеням и химической структуре, подчёркивается способность хронобиотиков усиливать или ингибировать ключевые компоненты циркадных часов, такие как белки CLOCK, BMAL1, PER и CRY. Особое внимание уделяется терапевтическому применению хронобиотиков, включая их потенциал для лечения нарушений сна, метаболических и возрастных десинхронозов. Обладая высокой чувствительностью и специфичностью, эти соединения являются перспективными инструментами поддержания физиологических ритмов, обеспечивающими здоровое старение и персонализированный подход к пациенту с нарушениями сна. Учитывая широкий потенциал для репозиционирования соединений, хронобиотики — перспективное направление, в том числе для внедрения экспериментальных соединений-корректоров циркадных ритмов в клиническую практику.

Полный текст статьи на русском языке доступен на сайте журнала (http://pbmc.ibmc.msk.ru).

Ключевые слова: хронобиотики; циркадные часы; циркадные ритмы; классификация; терапевтические перспективы; десинхроноз

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