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The Symbiosis of Circadian Rhythms and Oxidative Stress: Exploring Consequences and Opportunities

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Abstract

Oxygen and the synchronization of circadian rhythms are pivotal in orchestrating a myriad of physiological functions crucial for sustaining homeostasis. These include the modulation of blood pressure, the cyclical nature of sleep and alertness, and the intricate cellular communication networks essential for health and disease management. At the heart of circadian regulation lies a sophisticated intracellular chronometer, which primes organisms to predict and adapt to environmental fluctuations, aligning their physiological responses and behaviors to the optimal times of day. Under conditions of heightened stress, the capacity of human bodies or individual cells to maintain internal equilibrium, including the balance of redox states and the precision of circadian cycles, may become compromised. Such disruptions at the cellular and systemic levels can precipitate deleterious outcomes, paving the way for the onset of cardiovascular diseases, neurodegenerative conditions, and cancers. Recent strides in scientific research have deepened our grasp of the mechanisms underpinning circadian rhythms and the critical role played by various components of oxidative stress. The exploration of the molecular intersections between oxidative stress and circadian rhythm dysregulation has emerged as a key area of focus, illuminating the underpinnings of their interplay. Although there is a wealth of knowledge on the dynamics and significance of oxidative stress and circadian rhythms when considered separately, the nexus of their interaction remains relatively underexplored. This review endeavors to highlight the complex symbiotic interplay between these two systems in the maintenance of physiological integrity and their consequential roles in the pathogenesis of diseases. By targeting both the circadian and oxidative stress frameworks simultaneously, there emerges a promising avenue for enhancing disease management strategies, particularly for conditions that have their roots intertwined in both systems. Embracing this dual-focused approach marks a significant stride towards improving our capacity to alleviate diseases attributed to the misalignment of circadian rhythms and oxidative imbalances, heralding a new era in the prevention and treatment of such disorders.

Key words: Circadian rhythms, Oxidative stress, Reactive oxygen species

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Introduction:

Circadian rhythms play a crucial role in the dynamics of ecosystems, individual organisms, and cellular functions. These rhythms manifest as variations in physical, mental, and behavioral patterns that align closely with a 24-hour cycle (**Duffy and Wright, 2005).** Despite this cycle slightly exceeding an actual day and showing variation among individuals, it is widely regarded as a response to the Earth's rotation and its orbit around the sun, influencing daily shifts in light and temperature. Equally, the significance of oxygen in our universe and its contribution to various biological mechanisms cannot be overstated. Oxygen's role in maintaining life on Earth, particularly in humans, involves a delicate equilibrium of oxygen-related molecules. This intricate network includes a multitude of enzymes, bioactive compounds, and signaling molecules. Disruptions in the sophisticated biological functions of oxygen and circadian rhythms pose a threat to both the existence and quality of life. Evidence increasingly suggests a profound interconnection between these two fundamental processes **(Mazzoccoli et al., 2012).**

Cells have evolved intricate systems for energy production and signal transduction, relying heavily on oxygen and its derivatives, known as reactive oxygen species (ROS). A wealth of research has delved into ROS, revealing their dual role in promoting health and contributing to disease, alongside the cellular defenses developed to mitigate their detrimental effects. Notably, many of these protective mechanisms, including antioxidant synthesis and the production of defensive enzymes, exhibit rhythmic patterns in their regulation or expression. This points to a fascinating association between oxidative stress and circadian rhythms. Approximately 10% of the body's genes operate on a circadian schedule, impacting diverse physiological and biochemical functions. These genes are pivotal in vital cellular processes like cell division, proliferation, and DNA repair. Physiologically, circadian rhythms govern sleep/wake cycles, body temperature regulation, and T-cell immune responses. Disruptions in these rhythms can result in notable health issues at both the cellular and systemic levels. In the following sections, we explore the interplay between circadian rhythms and oxidative stress in biological systems, which are crucial in maintaining physiological equilibrium and in the emergence of certain diseases **(Bell-Pedersen et al., 2001).**

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Understanding the Molecular Basis of Circadian Rhythms:

Circadian rhythms are innate cycles of physical, mental, and behavioral changes observed in living beings. For a rhythm to be classified as circadian, it must exhibit five key characteristics: (i) it can be synchronized or entrained to the local environment, (ii) it continues autonomously even in the absence of external cues, (iii) its timing or phase can be adjusted, (iv) it follows a cycle approximately 24 hours in length, and (v) its periodicity remains consistent across a range of temperatures (**Bell-Pedersen et al., 2001**). To verify whether an expression pattern adheres to a circadian rhythm, data are typically modeled using a cosine wave approximation (known as the cosinor method) and represented graphically, as illustrated in Figure 1. A pattern that does not conform to this consistent wave-like form is likely not circadian.

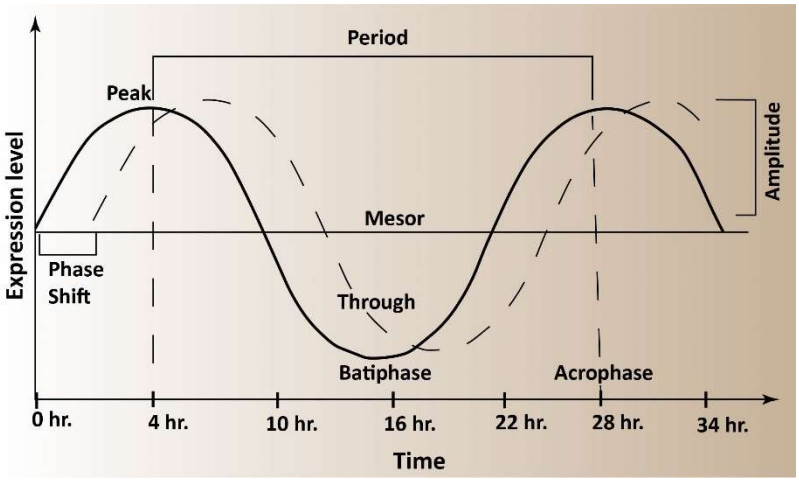

Figure 1: A model representing a circadian rhythm with a 24-hour period typically exhibits several characteristic features. These include the Peak = denotes the highest level of gene expression during the oscillation. Acrophase = representing the time at which the curve reaches its peak. Conversely, the Trough = the lowest level of gene expression, with the bathy phase denoting the time at which the curve reaches its nadir or trough. The period of the rhythm reflects the duration needed to complete one cycle, from one peak to the next. The mesor = positioned midway between the highest and lowest points of the curve, provides an estimating statistic of rhythm. The amplitude measures the distance from the mesor value to the zenith or peak, while the phase shift indicates the displacement of the curve along the time axis. These parameters collectively define the characteristics of a circadian rhythm model.

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Circadian rhythms are shaped by external cues, or zeitgebers, including light, diet, exercise, and temperature variations. Light is the paramount zeitgeber, setting the body's clock through signals processed by the suprachiasmatic nucleus (SCN) in the hypothalamus, which then orchestrates the timing across the organism **(Golombek and Rosenstein, 2010).** While light is a primary external trigger, the SCN also responds to internal cues like serotonin and melatonin, integral for feedback regulation rather than rhythm initiation **(Meyer-Bernstein and Morin, 1996; Mintz et al., 1997).** Beyond these, a complex network involving hormones such as insulin and glucocorticoids plays a critical role in harmonizing these biological rhythms, a process elegantly depicted in Figure 2 **(Sahar and Sassone-Corsi, 2012**; **Saini et al., 2011).**

While the central pacemaker is situated in the SCN region of the hypothalamus, individual cells throughout the body harbor their own internal clocks, which synchronize in response to external signals **(Nagoshi et al., 2004).** These clocks operate through a transcriptional-translational feedback loop. The positive arm involves proteins like aryl hydrocarbon receptor nuclear translocator-like (ARNTL), also known as BMAL1 (Brain and muscle arnt like 1), and circadian locomotor output cycles kaput protein (CLOCK) **(Antoch et al., 1997; Gekakis et al., 1998).** In contrast, the negative arm consists of period homologs 1–3 (PER1–3) and cryptochrome 1 and 2 (CRY1 and 2) **(Kume et al., 1999).** In Figure 3, the circadian cycle begins with the formation of a heterodimer between BMAL1 and CLOCK. This interaction prompts the binding of BMAL1 and CLOCK to E-box elements within gene promoters, initiating the transcription of various rhythmic proteins, including the PERs and the CRYs. Following this, a heterodimer forms between PER and CRY proteins, facilitating their translocation into the nucleus. Once there, they disrupt BMAL1 and CLOCK activity at promoter sites, thus concluding the cycle **(Shearman et al., 2000)**. After the degradation of PER-CRY proteins, BMAL1-CLOCK is no longer inhibited, initiating the cycle anew. This cycle length has evolved to align with the duration of a day. Light, the primary external cue, indirectly influences the SCN, synchronizing the molecular clock with the day-night cycle.

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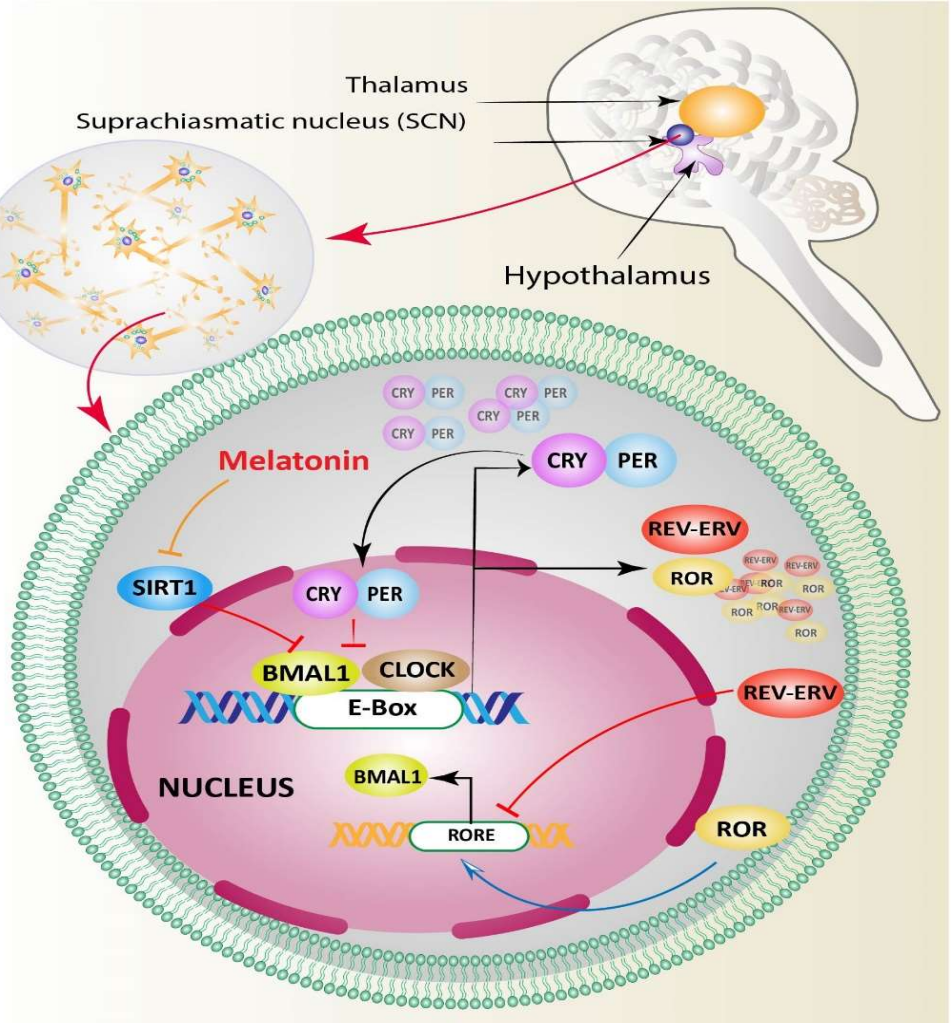

Figure 2: SIRT1 and melatonin play crucial roles in the molecular mechanism of the circadian clock. The basic circadian mechanism involves a transcriptional-translational feedback loop, where CLOCK and BMAL1 form a heterodimer and regulate the expression of target genes like Periods (PER) and cryptochromes (CRY). SIRT1 disrupts this process by inhibiting BMAL1, activity and. Melatonin inhibits SIRT1 expression and activity, preventing BMAL1 inactivation. Additionally, an auxiliary loop involves clock-controlled proteins like REV-ERBs and RORs, which regulate BMAL1 expression through competitive binding to specific sites on its promoter. While REV-ERBs inhibit BMAL1 transcription, RORs promote it, contributing to the regulation of circadian rhythms.

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The regulation of BMAL1 and CLOCK involves an additional regulatory loop in the core circadian mechanism. Orphan nuclear receptors REV-ERBα and β repress BMAL1 transcription by binding to retinoic acid-related orphan receptor-response elements (ROREs) in the BMAL1 promoter. REV-ERBα also suppresses CLOCK transcription (14). Competing with REV-ERBs for RORE-binding sites in the BMAL1 promoter are RAR-related orphan receptors (RORs) α, β, and γ, which activate BMAL1 transcription (**Guillaumond et al., 2005**, **Sato et al., 2004).** Like the PERs and the CRYs, REV-ERBs and RORs are clock-controlled, forming a stabilizing feedback loop. However, the circadian regulation of individual RORs varies: RORα expression oscillates only in the SCN, RORγ expression oscillates only in peripheral tissue, and the circadian status of RORβ expression is currently unknown **(Sato et al., 2004).** The activity of REV-ERBβ, a key regulator of BMAL1 and CLOCK, is intriguingly influenced by its redox state. This protein's function is enhanced through heme binding, which facilitates its interaction with a histone deacetylase (HDAC), activating REV-ERBβ. Notably, the reduced (dithiol) form of REV-ERBβ binds heme more effectively than its oxidized **counterpart (Gupta and Ragsdale, 2011)**. Given that reactive oxygen species (ROS) can oxidize thiol groups, it's hypothesized that oxidative stress might dampen REV-ERBβ activity, potentially upregulating BMAL1 and CLOCK expression and thus impacting circadian rhythms—an effect yet to be empirically verified.

Cellular Antioxidant System Dynamics: A Patterned Shield

Reactive Oxygen Species (ROS) like superoxide radicals (O2-), peroxides (ROOR), and hydroxyl radicals (OH-) are natural by products of the complex chemical reactions occurring within cells, predominantly within the mitochondria. These molecules are not merely waste products; they serve pivotal roles in defending the cell and facilitating crucial biological functions **(Bridges et al., 1992; Brigelius-Flohe et al., 2011).** Notably, superoxide radicals and hydrogen peroxide stand out for their involvement in cellular communication, influencing a broad spectrum of biological activities including the activation of kinases and the regulation of insulin, among others **(Bartosz, 2009).** Their unique properties make ROS prime candidates for signaling molecules, playing roles in numerous pathways essential for cellular function. However, the cellular benefits of ROS come with a caveat; their levels must be carefully managed. Uncontrolled ROS can cause significant damage, disrupting cellular integrity and

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function. To prevent such damage, cells employ an intricate defense mechanism comprising enzymes like catalases, superoxide dismutases, and glutathione peroxidases, alongside naturally occurring antioxidants including Vitamins C and E, glutathione, and uric acid **(Hardeland et al., 2003; Mates et al., 1999).** These systems work in concert to neutralize excess ROS, maintaining a delicate balance essential for health and vitality. This sophisticated interplay ensures that ROS fulfill their beneficial roles without compromising cellular health, illustrating the cell's remarkable ability to harness potentially harmful agents for critical biological processes.

Emerging research underscores the circadian regulation of protein expression as a pivotal factor in cellular defence against oxidative stress. Studies have revealed diurnal variations in DNA damage, lipid peroxidation, and protein oxidation, highlighting the daily fluctuations in oxidative stress response. This is closely tied to the rhythmic expression of antioxidants and protective enzymes, suggesting a potential for more targeted antioxidant **strategies (Kanabrocki et al., 2002; Edmunds et al., 1987)**. Specifically, superoxide dismutases (SODs), crucial in mitigating oxidative harm by converting superoxide radicals into oxygen and hydrogen peroxide, display circadian patterns in activity and expression. In eukaryotic cells, two primary forms of superoxide dismutases (SODs) play critical roles in combating oxidative stress: the copper/zinc (Cu/Zn) SOD, located in both the cytoplasm and extracellular spaces, and the manganese (Mn) SOD, situated within mitochondria **(Perry et al., 2010).** The mitochondrial Mn SOD is particularly crucial for cellular redox balance due to its location in the mitochondria, the primary site of reactive oxygen species (ROS) production. This enzyme has a significant impact on managing specific ROS levels. The circadian variation in SOD activity, highlighting its peak during the nocturnal phase, was initially identified by Diaz-Munoz and colleagues in 1985 within the rat cerebral cortex. This peak coincides with increased levels of malondialdehyde, a marker of lipid peroxidation, illustrating a temporal regulation in antioxidant defense mechanisms **(Diaz-Munoz et al., 1985).** Notably, these patterns vary across different tissues and are influenced by the core molecular circadian machinery. Following SOD activity, catalase (CAT) further neutralizes hydrogen peroxide, with its activity also exhibiting diurnal peaks. These rhythms in antioxidant enzyme activities suggest a sophisticated circadian coordination in cellular defenses against oxidative damage, varying between nocturnal and diurnal organisms to align with their unique physiological rhythms (**Sani et al., 2006**).

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Glutathione (GSH) serves as a potent antioxidant, countering reactive oxygen species (ROS) through the action of selenium-dependent glutathione peroxidase (GPx) proteins, which convert GSH to its oxidized form, glutathione disulfide (GSSG). Subsequently, glutathione reductase (GR) reduces GSSG back to GSH, enabling further ROS neutralization **(Mannervik, 1987).** An integral component of the GSH system, glutathione S-transferases (GSTs), encompassing various isoforms, plays a crucial role in mitigating oxidative stress by deactivating harmful by products like α,β-unsaturated aldehydes and quinones **(Hayes et al., 2005; Atkinson and Babbitt, 2002).** Circadian fluctuations in GSH levels were initially observed in rat blood in 1967, with subsequent studies confirming these oscillations across different species, including rodents, crayfish, and humans (**Atkinson and Babbitt, 2002; Baydas et al., 2002; Calcutt, 1967; Fanjul-Moles et al., 2009**). Moreover, GSSG, GPx, GR, and GST enzymes also exhibit daily expression patterns. Interestingly, while rodents typically peak in GSH expression during the light phase, humans exhibit peak levels at the end of the night **(Sani et al., 2006).** This divergence mirrors differences in circadian rhythms between nocturnal and diurnal species, akin to variations observed in catalase (CAT) activity. Notably, in the rat cerebral cortex, the peak expression of GSH and GPx aligns with lipid peroxidation levels, suggesting a coordinated response to oxidative stress.

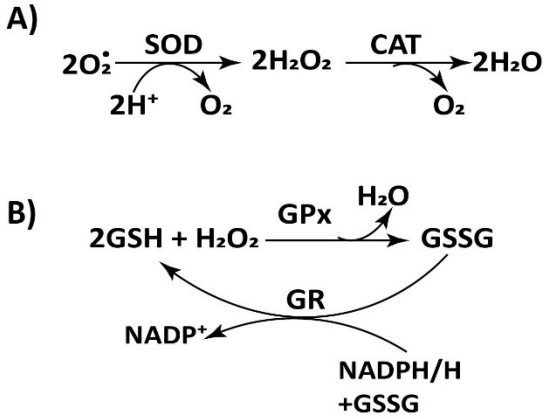

Figure 3: Enzymatic decomposition of superoxide (O2-) involves the catalysis of SOD, which converts superoxide into hydrogen peroxide (H2O2), releasing oxygen in the process. H2O2 is further broken down to water by enzymes like catalases (CAT), or peroxidases such as GPx. In the GSH system, H2O2 reacts with two molecules of glutathione (GSH) catalyzed by GPx, resulting in the decomposition of H2O2 into water and oxidized glutathione (GSSG). GSSG is

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then reduced back to GSH by GR, utilizing NADPH as a hydrogen donor.

Interplay Between Circadian Rhythms and Oxidative Stress

Research has intricately linked the mechanisms of circadian rhythms with the body's antioxidative defenses, unveiling a sophisticated interplay between biological timing and cellular resilience against oxidative stress. A compelling study with Drosophila melanogaster, commonly known as fruit flies, illuminated this complex relationship, revealing that these organisms encounter heightened susceptibility to oxidative damage during daylight hours, evidenced by increased protein degradation and a spike in mortality rates when exposed to hydrogen peroxide. This temporal vulnerability underscores the circadian clock's pivotal role in modulating the organism's defense mechanisms **(Jaeschke and Wendel, 1985).** In a striking demonstration of the circadian rhythm's influence, fruit flies deficient in the PER protein, a crucial component of the circadian clock, did not exhibit the same time-dependent fluctuation in mortality rates following oxidative challenge, cementing the circadian system's contribution to protective responses against oxidative stress. Furthermore, experiments disrupting the natural light-dark cycles, such as constant light exposure, obliterated the time-of-day differences in mortality, reinforcing the essential function of circadian rhythms in orchestrating the body's antioxidative defenses. This phenomenon, mirrored in mammalian studies, notably in Syrian Hamsters, further corroborates the profound connection between circadian rhythms and the dynamism of oxidative stress defense mechanisms, highlighting the elegant complexity of biological systems in mitigating cellular harm **(Krishnan et al., 2008).**

Circadian rhythms and oxidative stress are intertwined through key factors that play significant roles in both processes. Melatonin, a hormone primarily produced by the pineal gland, was first identified for its circadian oscillation in 1964. However, its antioxidant properties weren't recognized until nearly three decades later. Since then, researchers have extensively explored and utilized melatonin's antioxidant capabilities across various **fields (Quay, 1964; Radogna et al., 2010).**

Another crucial factor, SIRT1, has emerged as a link between oxidative stress and circadian rhythms. SIRT1 influences oxidative stress responses by activating downstream effectors such as p53 and FOXO transcription factors **(Vurusaner et al., 2012).** Additionally, studies in 2008

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revealed SIRT1's involvement in the core circadian mechanism through the deacetylation of proteins like BMAL1 and PER2 **(Nakahata et al., 2008).** Melatonin and SIRT1 interact, with melatonin inhibiting both the expression and activity of SIRT1, creating a feedback loop between melatonin, circadian rhythms, and oxidative stress **(Jung-Hynes et al., 2010; Jung-Hynes et al., 2011).**

Moreover, NAD+ and its derivative, NADH, are essential in facilitating oxidation in redox reactions, whereas NADP+/NADPH drives reduction reactions. These reactions include critical processes like the conversion of GSSG to GSH and the generation of O2- through the transfer of electrons from NADPH via NADPH oxidase **(Houtkooper et al., 2010).** SIRT1's involvement in both oxidative stress and circadian rhythms is reinforced by nicotinamide adenine dinucleotide (NAD+). SIRT1 depends on NAD+ as a cofactor for protein deacetylation, thereby making its functionality reliant on the availability of NAD+. The circadian clock regulates the synthesis of NAD+, and its production diminishes with age and exposure to oxidative stress. Among the oscillating clocks is the heterodimeric complex formed by core circadian transcription factors BMAL1 and CLOCK. This complex governs the Nampt gene, responsible for encoding the essential NAD+ biosynthetic enzyme nicotinamide phosphoribosyl transferase (NAMPT). NAMPT catalyzes the production of NAD+ and influences SIRT1 activity in peripheral tissues **(Ramsey et al., 2009).** Consequently, NAD+ plays a crucial role in regulating circadian rhythms through its function as a coenzyme for SIRT1. (**Houtkooper et al., 2010**). Consequently, the onset of oxidative stress and the overall cellular redox status influence the availability of NAD+, thereby impacting SIRT1 activity. Additionally, both NADH and NADPH enhance the DNA binding ability of CLOCK:BMAL1 and NPAS2:BMAL1 heterodimers to their transcriptional targets, while NAD+ and NADP+ inhibit this activity. This direct correlation emphasizes the significance of the redox status of NAD+/NADH and NADP+/NADPH in regulating circadian rhythms **(Rutter et al., 2001).** Though the exact links between circadian rhythms and oxidative stress are not fully understood, researchers and physicians utilize this relationship through chronotherapy. This approach involves administering medication in sync with the body's natural rhythms to enhance efficacy and minimize side effects. Studies have shown improved outcomes in diseases like diabetes, hypertension, rheumatoid arthritis, and cancer when treatments are timed to align with circadian rhythms. This strategy holds promise for various other conditions,

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suggesting potential benefits in managing diseases like asthma and Parkinson's disease **(Bruguerolle and Simon, 2002; Burioka et al., 2010; Cutolo, 2012; Kanat, 2007; Wilking et al., 2013).**

Conclusion:

Oxidative stress and circadian rhythms have been extensively studied for over five decades across various scientific fields, given their fundamental roles in cellular function. While both processes are implicated in numerous diseases, a comprehensive understanding of the cause-and-effect relationship between circadian rhythm and oxidative stress signaling remains lacking. Further research, particularly in appropriate model systems, is imperative to elucidate this association. However, utilizing rodent models presents a challenge due to differences in their circadian patterns compared to humans. Nevertheless, insights gleaned from rodent studies can be adapted to human relevance. Additionally, the intricate nature of antioxidant enzyme families poses hurdles in identifying specific isoforms responsible for rhythmicity. Nonetheless, evidence suggests that at least one form of each enzyme is rhythmically regulated, impacting disease pathologies. To effectively address diseases involving both circadian rhythm and oxidative stress, a holistic approach targeting both components holds promise. For instance, integrating antioxidants with circadian rhythm-resynchronizing strategies such as melatonin may yield favorable outcomes. Collaborative efforts among researchers across diverse disciplines will be crucial in advancing our understanding and translating findings into effective clinical interventions. Ultimately, by delving deeper into the intricate interplay between oxidative stress and circadian rhythms, we can pave the way for innovative approaches to disease prevention and treatment in the future.

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