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REVIEW

Circadian Rhythms and Pain: A Narrative Review on Clock Genes and Circadian-Based Interventions

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Abstract: Pain is a common symptom of many diseases and seriously affects the quality of life. Circadian rhythm is the regular, cyclical physiological, biochemical, and behavioral changes that occur within a 24-hour period in biological organisms, primarily regulated by clock genes. Pain sensitivity may have circadian rhythms, with clock genes likely influencing this pain-related rhythmicity. Therefore, restoring normal circadian rhythms and regulating the expression of clock genes are regarded as viable strategies to combat the development of pain. First, this review elucidates the core operational mechanisms of clock genes. Second, it also discusses the relationship among multiple types of pain and clock genes, such as sciatic nerve injury, inflammatory pain, chemotherapy-induced neuropathic pain, headache, the pain of Restless Legs Syndrome and fibromyalgia. Third, it presents the pain treatment and pain management strategies based on the current research on circadian rhythms. Exploring the role of circadian rhythm in pain can help increase our understanding of pain and have significant clinical implications for pain patients.

Plain Language Summary: The core of the circadian rhythm is driven by genes such as *Per, Cry, Bmal1, Clock, Npas2* and *Rev-erbα*, and abnormal expression of these genes is directly associated with sciatic nerve injury, inflammatory pain, chemotherapy-induced neuropathic pain, headache, the pain of Restless Legs Syndrome and fibromyalgia.

This study focuses on the mechanisms of the circadian rhythm, the relationship between clock genes and pain, as well as the applications of the circadian rhythm in pain management and treatment.

Pain can be alleviated through chronotherapy, clock gene-based therapies and Traditional Chinese Medicine to regulate clock genes and suppress inflammatory factors. Future research on circadian rhythms and pain may provide more comprehensive solutions for pain management and treatment.

Keywords: clock genes, pain management, the core mechanism of circadian rhythm, chronotherapy

Introduction

The International Association for the Study of Pain recently published a new definition of pain,[1] " Pain: An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage". Pain, typically from tissue damage or disease, includes acute pain (eg, trauma, inflammation) and chronic pain (eg, nerve injury, cancer, immune disorders). Apart from ongoing pain, patients may have heightened pain to equivalent stimulation, this enhanced stimulus-dependent pain is called hyperalgesia.[2] Current research has found that pain sensitivity exhibits a circadian rhythm, with its intensity varying throughout the day; in some diseases, pain sensitivity peaks during the daytime, such as migraine[3] and rheumatoid arthritis[4] acute ischemic syndromes of unstable angina patients' pain occurs in the morning, but some patients experience more intense pain at night, and this pattern is commonly observed in biliary colic[5] or osteoarthritis.[6] And terminally-ill cancer[7] patients typically suffer pain in the afternoon and evening.

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Circadian rhythm refers to the periodic physiological, biochemical, and behavioral changes exhibited by living organisms over an approximate 24-hour cycle. Circadian rhythms are self-sustained, endogenous oscillations generated by clock genes that persist with a period of around 24-hours under constant conditions.[8] These rhythms partially contribute to regulating various physiological processes in organisms, such as sleep-wake cycles, blood pressure, body temperature, hormone levels, and pain sensitivity, to ensure synchronization with environmental cycles.[9–11] Recent investigations indicate that circadian rhythms[12] and clock genes might play a crucial role in the progression of pain. Abnormal expressions and rhythm disorders of clock genes have been discovered in multiple pain models. Animals with clock gene knockouts, such as period2 (*Per*$2^{-/-}$ mice),[13] do not develop tactile pain hypersensitivity even following peripheral nerve injury. Since the molecular mechanisms involved in the research of circadian rhythm and pain still require further investigation, Therefore, this review summarizes the core mechanisms of circadian rhythm, then reviews the existing studies on clock genes in the occurrence and development of pain, and finally explores the current research progress of pain management related to circadian rhythm. We hope to deepen our understanding of pain pathogenesis from the perspective of clock genes, to interpret their potential value in pain management strategies, and thereby to improve the clinical management of patients with pain.

Literature Search Strategy

Studies cited in this review were searched on PubMed database up to April 2025. Using the following keywords: "pain", "circadian rhythm", "clock genes", "pain management", "period(Per)", " ARNT like-1(Bmal1)", " circadian locomotor output cycles kaput(Clock)", " cryptochrome(Cry)", " neuronal PAS domain protein 2(Npas2)", " nuclear receptor subfamily 1, group D, member 2 (Nr1d2, also called Rev-erbα)". The search results were further filtered based on the title and abstract, and more articles were retrieved using the PubMed function for tracking related articles. Subsequently, studies that did not cover pain and circadian rhythm were eliminated after thoroughly reading the full text.

The Core Mechanism of Circadian Rhythm

Suprachiasmatic Nucleus (SCN)—The Master Circadian Clock

The circadian rhythm is closely related to human daily life, with the most prevalent physiological activity being the alignment of waking at sunrise and resting at sunset. This cyclical behavioral pattern has evolved over millennia in humans. In mammals, the central circadian pacemaker is located in the SCN.[14] The Earth's rotation generates a 24-hour cycle of light and darkness, with this photic information being relayed along the retinohypothalamic tract to the SCN. Subsequently, the SCN modulates clock gene expression across various tissues and organs through intricate feedback loops, ensuring that internal circadian rhythms align with external temporal changes (Figure 1). When it comes to circadian rhythm, the core revolves around clock genes, including *Per, Cry, Bmal1, Clock, Npas2*, and *Rev-erbα*, which exist in every cell of all mammals.[15,16] The rhythmic output signals of SCN can precisely regulate the biological clocks in peripheral tissues, allowing them to carry out corresponding physiological activities within appropriate timeframes.[17]

The Choroid Plexus Is an Important Circadian Clock Component

The choroid plexus (ChP) is a key brain structure that produces cerebrospinal fluid, maintains the blood-cerebrospinal fluid barrier, regulates brain homeostasis and circadian rhythms, and is located in the four ventricles of the brain.[18,19] Jihwan Myung et al found in mice that the ChP can independently regulate rhythms and transmit signals to SCN through cerebrospinal fluid, shortening its rhythm cycle to a near behavioral rhythm. Moreover, the clock genes such as Bmal1and Per2 exhibit stronger amplitudes, greater intensities, and shorter oscillation periods in ChP than those in SCN.[20]

Peripheral Clocks

Peripheral clocks are the biological clocks present in peripheral tissues, which together with the central clock (SCN) constitute the complete circadian system. Although peripheral clocks are mainly regulated by the SCN, they still possess autonomous circadian rhythms.[21] Studies have found that SCN lesions reduce the overall rhythmic amplitude without eliminating basal oscillations in the liver.[22] Therefore, the rhythms of some important peripheral organs may tick independently of their master.

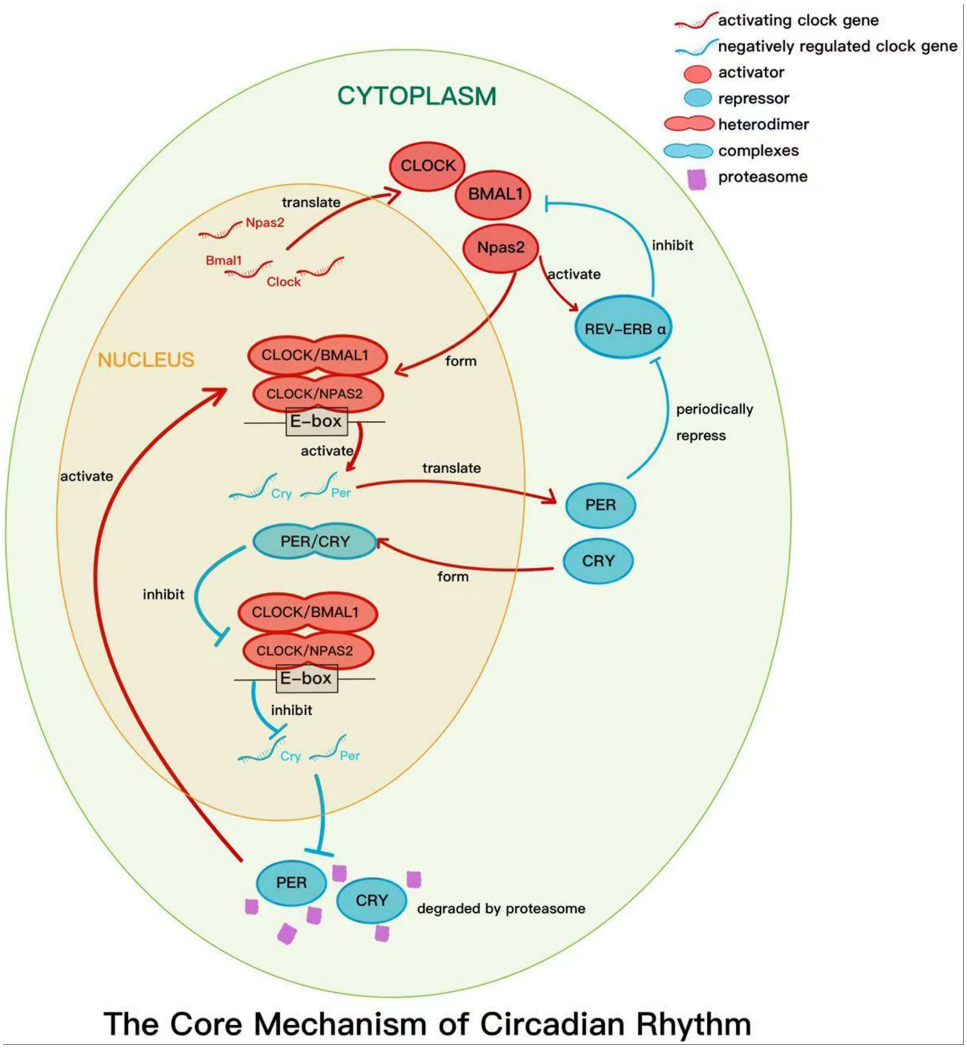

Figure 1 The Core Mechanism of Circadian Rhythm.

The Regulatory Mechanism of the Circadian Rhythm

In 1984, Michael Rosbash et al transduced the *Per* gene fragment into the genome of arrhythmic $Per^{-/-}$ flies to restore circadian rhythms of locomotor behavior, thereby indicating the presence of clock genes.[23] In 1988, Kathleen et al found that the expression level of the *Per* gene significantly rose at night, while it decreased conspicuously during the day. This phenomenon reflected the existence of circadian rhythm genes in drosophila.[24] Subsequently, it was found that PER/CRY, CLOCK/BMAL1[25] and CLOCK/NPAS2[26] all play predominant roles in TTFLs in the form of heterodimers. Among them, PER/CRY acts as a negative regulator in the TTFLs, while CLOCK/BMAL1 and CLOCK/NPAS2 serve as transcriptional activators in the TTFLs. Taking the transcription of *Clock, Bmal1*, and *Npas2* in the nucleus as the starting point of the circadian rhythm, the proteins transcribed from these genes form CLOCK/BMAL1 and CLOCK/NPAS2 form heterodimers in the cytoplasm. Subsequently, these heterodimers enter the nucleus and bind to E-boxes, thereby activating the transcription of *Crys* and *Pers*. As PERs and CRYs accumulate in the cytoplasm, they form PERs/CRYs complexes that enter the nucleus and bind to CLOCK/BMAL1 and CLOCK/NPAS2 heterodimers, inhibiting the transcription of CLOCK/BMAL1, CLOCK/NPAS2 heterodimers, and suppressing the transcription of *Pers* and *Crys*.[25] With the degradation of the PER/CRY complexes,[27,28] the transcriptional activity of the CLOCK/BMAL1 heterodimer gradually recovers, initiating a new cycle of the circadian rhythm.

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The orphan nuclear receptor REV-ERBα was involved in the TTFL and formed an additional feedback loop.[29] In 2002, Nicolas Preitner et al delineated the TTFL into two distinct components: the Positive limb, which comprises transcription factors such as BMAL1 and CLOCK, and the Negative limb, consisting of proteins like PER and CRY; they identified the REV-ERBα as a key regulator that links these two limbs, specifically, the PER and CRY proteins periodically repress *Rev-erbα* transcription, while BMAL1 and CLOCK cyclically activate it, leading to periodic accumulation of REV-ERBα. This, in turn, inhibits *Bmal1* and *Clock* transcription, forming a feedback loop. Thus, REV-ERBα is a crucial factor driving the cyclical transcription of BMAL1 and CLOCK, which serves as one of the fundamental bases for periodic fluctuations in biological clocks(Figure 1).[30]

Clock Genes and Pain

A clear bidirectional relationship exists between pain and circadian rhythm disruption.[31] On one hand, pain can interfere with the normal circadian rhythm;[32] on the other hand, the disorder of the circadian rhythm itself may also serve as an important inducing factor for pain,[33] further highlighting the complexity of the interaction between the two. The abnormal expression of clock genes is precisely a key aspect in this complex correlation and may profoundly influence the occurrence and development of pain (Table 1).

Clock Genes and Pain Caused by Nerve Injury

A significant proportion of pain symptoms arises directly from nerve injury. Norimitsu Morioka's team found that the actions of neurotransmitters NA (Noradrenaline) and 5-HT (5-Hydroxytriptamine) in the spinal dorsal horn of partial sciatic nerve ligation (PSNL) mice may be downregulated, which leads to a decrease in the expression of *Per1* in astrocytes.[42] It is noteworthy that downregulation of *Per1* lead to pain through JNK phosphorylation and CCl2-CCR2-dependent pathway in spinal cord astrocytes.[32] Consequently, they put forward the hypothesis that perhaps a novel and effective therapeutic approach for chronic neuropathic pain could be identified by restoring the expression of *Per1*.[43]

However, the modulation of pain by members of the PERs family is not consistent. In a recent study conducted by Wakaba Yamakawa et al, it was observed that expression of the α1D-adrenoreceptor (α1D-AR) in the spinal cord of *Per2*$^{-/-}$ mice were elevated, resulting in increased production of the endogenous cannabinoid receptor ligand 2-arachidonoylglycerol (2-AG),

Table 1 Clock Genes and Pain

Pain-Causing Disease	Research Object	Research Site	Related Clock Genes	Clock Genes and Pain	References
Nerve injury	PSNL mice PSLPer2$^{-/-}$mice	Spinal cord Spinal cord	**Per1** **Per2**	Downregulation of *Per1* expression causes pain *Per2* knockout inhibits hyperalgesia	[13,32]
Rheumatoid arthritis	RA synovial cells RA mice	Synovial cells Synovial cells Blood	**Per2** **Per2** **Cry**	Downregulation of PER2 protein expression Circadian rhythm of PER2 protein is disrupted *Cry1* and *Cry2* knockout leads to increased levels of inflammatory mediators, exacerbating arthritis pain	[34,35]
Fibromyalgia	FM patient	Blood	**Per3**	Per3 gene variation is associated with susceptibility to fibromyalgia	[36]
Restless Legs Syndrome	RLS mice	Spinal cord	**Clock, Per1, Per2, Bmal1, Per3, Cry**	During daytime, *Clock* and *Per1* expression are downregulated, while *Per2* expression is upregulated At night, the expression of *Clock, Bmal1, Per1, Per2, Per3, Cry1*, and *Cry2* is downregulated	[37]
Opioid-induced hyperalgesia	OIH mice OIHNpas2$^{-/-}$mice	TG, NAc –	**Per2, Per3, Cry, Dbp, Ciart, Bmal1 Npas2**	*Per2, Per3, Cry, Dbp*, and *Ciart* are significantly upregulated *Bmal1* is significantly downregulated *Npas2* knockout increases hyperalgesia in male mice	[38,39]
Induced peripheral neuropathy	CIPN Rat	DRG	**Per2**	Pain leads to lengthening of the *Per2* circadian rhythm cycle	[40]
Headache	NTGPer1$^{-/-}$Per2$^{-/-}$mice	–	**Per1, Per2**	*Per1* and *Per2* knockout results in increased pain threshold	[41]

which inhibited neuropathic pain hypersensitivity.[13] This result reveals the role of *Per2* in neuropathic pain and suggests that *Per2* may participate in the regulation of neuropathic pain through the endogenous cannabinoid system.

Clock Genes and Inflammatory Pain

Rheumatoid arthritis (RA) is a disease characterized by a typical circadian rhythm in its clinical manifestations, particularly in the morning exacerbation of inflammatory symptoms such as joint swelling, stiffness, and pain, which tend to be relieved in the afternoon.[44] Hwayoung Lee[34] demonstrated that the after treating primary cultured rheumatoid synovial cells with LPS for 12h and 24 h, the expression of PER2 protein in the cells was significantly reduced. Akira Hashiramoto[45] discovered that PER2 circadian rhythm was normal in wild-type (WT) mice but disrupted in synovial cells of the foot joints of arthritis mice. In addition, this study also found that arthritis may potentially disrupt the rhythm of multiple clock genes in the spleen.

To further explore the impact of clock genes on arthritis, they used $Cry1^{-/-}$ $Cry2^{-/-}$ mice to establish an arthritis model and found that the symptoms of $Cry1^{-/-}$ $Cry2^{-/-}$ arthritis mice were significantly aggravated compared to arthritis WT mice, including proliferation of the synovial lining cells, infiltration of lymphocytes, and cartilage destruction. Comparing the levels of IL-1β, IL-6, TNF-α and MMP3 in the serum of arthritis $Cry1^{-/-}Cry2^{-/-}$ mice and arthritis WT mice on the 14th day, they revealed the levels of inflammatory mediators in $Cry1^{-/-}Cry2^{-/-}$ arthritis mice were significantly higher than those in arthritis WT mice. Given that IL-6[46] and IL-1β[35] serve as pro-inflammatory drivers of pain, the absence of the *Cry* gene is suggested to exacerbate the pain associated with arthritis.

In polymyalgia rheumatica, pain also exhibits a typical circadian rhythm similar to that of rheumatoid arthritis, with the most severe joint stiffness, swelling, and pain occurring in the early morning. By measuring the concentration changes of TNF-α and IL-6 in patients' plasma, it was found that the concentrations of these pro-inflammatory cytokines showed a positive correlation with the severity of pain and stiffness symptoms in patients.[47]

Clock Genes and Fibromyalgia

Fibromyalgia (FM) is a syndrome characterized by generalized body pain, often accompanied by sleep dysfunction, fatigue, mood disturbances, and physical impairment.[48] The key to distinguishing inflammatory pain from FM pain lies in differences in their pathological mechanisms: the former is primarily driven by peripheral inflammation, while the latter stems from augmented central pain processing (central sensitization) in the central nervous system.[49] In Silvia M. Bigatti et al's clinical study on FM patients, it was found that sleep disorders are common among fibromyalgia patients, with over 90% of patients experiencing disruptions in sleep rhythms.[50] Ariel B. Neikrug et al analyzed activity rhythms and sleep parameters in FM patients and concluded that circadian rhythm disturbances (low Amplitude, delayed Phi) are significantly associated with sleep disturbances and fibromyalgia symptoms (pain, fatigue, mood disturbance).[48] By comparing 24-hour urinary 6-sulfatoxymelatonin (aMT6s) levels among patients with FM and healthy controls, it was found that melatonin (specifically the disruption in daytime secretion rhythm) was significantly associated with reduced pain pressure threshold, larger number of trigger points and worse sleep quality in FM patients.[51] Sidrah Parvez et al conducted a correlation analysis between *Per3* polymorphism and clinical symptoms in patients with fibromyalgia syndrome and found a significant association between *Per3* variation and susceptibility to fibromyalgia syndrome. *Per3* polymorphism (rs57875989) may influence the development of fibromyalgia syndrome by affecting sleep-wake patterns, hormonal balance, and pain perception.[36]

Clock Genes and Pain Induced by Restless Legs Syndrome

Clock genes affect the changes of neurotransmitters in the central nervous system, contributing to the development of pain. Restless Legs Syndrome (RLS), as a central nervous system disorder, manifests in patients as severe static mechanical hyperalgesia.[52] Celia Piña-Leyva et al created a model of RLS[53] by lesioning dopaminergic neurons in the hypothalamic A11 nucleus through the injection of 6-hydroxydopamine (6-OHDA). They found that the pathology of hypothalamic A11 reduced the tissue content of dopamine (DA) in the lumbar spinal cord, resulting in the disappearance of the circadian rhythm of the paw withdrawal threshold (PWT) and a decrease in PWT during the daytime, which induced abnormal tactile pain. During the daytime, 6-OHDA reduced the expression of Clock and Per1 in spinal cord, but

increased the expression of *Per2*. At night, 6-OHDA diminished *Clock, Bmal1, Per1, Per2, Per3, Cry1*, and *Cry2* in spinal cord.[37] These results indicate that the circadian rhythm of PWT may result from the regulation of the DA system by clock genes in spinal cord.

Clock Genes and Opioid-Induced Hyperalgesia

One of the primary side effects associated with opioid use is hyperalgesia, specifically referred to as opioid-induced hyperalgesia (OIH). ZhangPan et al employed RNA-Seq technology to conduct sequencing analysis on the trigeminal ganglion (TG) and nucleus accumbens (NAc) which are related to pain signaling in OIH mice. By comparing the gene expression profiles of TG and NAc between OIH mice and control mice, they identified that *Ciart, Per2, Per3, Cry1, Cry2* and *Dbp* were significantly upregulated in OIH mice, while *Bmal1* exhibited downregulated.[38] Stephanie Puig's et al research concentrated on elucidating the role of the *Npas2* in fentanyl-induced hypersensitivity resulting from prolonged exposure, and they discovered that compared with wild-type males, only male *Npas2*$^{-/-}$ mice demonstrated a significant increase in fentanyl-induced hyperalgesia.[39] The above results suggest that the clock gene is closely related to opioid-induced hyperalgesia.

Clock Genes and Chemotherapy-Induced Neuropathic Pain

It is well established that agents such as paclitaxel can induce chronic neuropathic pain in cancer patients, significantly compromising their quality of life in the context of chemotherapy-induced peripheral neuropathy (CIPN).[54] Hee Kee Kim et al established a rat model of CIPN and demonstrated that the mechanical allodynia resulting from CIPN exhibits a circadian rhythmicity. They further used *Per2*::LucSV circadian reporter mice, monitored reporter bioluminescence of dorsal root ganglion (DRG) neurons in vitro, and they observed paclitaxel treatment significantly lengthened DRG circadian periods of *Per2*, but had little effect on the amplitude of oscillation. RNA-seq demonstrated that between the vehicle and paclitaxel treated rats at ZT8 and ZT20 revealed 522 and 832 diurnal differential expressed genes in the DH and the DRG, respectively. Functional enrichment analysis showed strong enrichment of angiogenesis and glomerulus development pathways in the DH and muscle contraction, blood vessel morphogenesis and cell–cell adhesion pathways in the DRG.[40]

Clock Genes and Headache

Headache is a type of neurological disorder with complex pathological mechanisms. Among them, migraine and cluster headache (CH) have attracted much attention due to their periodic attack characteristics which are closely related to circadian rhythms. Migraine attacks typically increase in frequency between 4:00 am and 9:00 am.[55] Currently, research on the association between clock genes and migraine remains limited. However, some new studies are exploring how genes and environment might work together on migraine—for instance, the *Clock* variation (such as the rs10462028 single nucleotide polymorphism) itself does not directly affect the risk of migraines; instead, when they interact with long-term stress resulting from economic difficulties, they may regulate the susceptibility to migraines, and the direction of this effect depends on the degree of economic stress.[56] And in CH, both episodic and chronic patients have a circadian rhythm in headache attacks, with a peak from midnight to early morning and a trough from noon to afternoon.[57] However, current research on clock genes shows that neither the *Clock* T3111C[58] nor the *Per3* VNTR polymorphisms are associated with cluster headaches. But higher proportions of sleep disorders and shift work in CH patients suggest the circadian clock system may contribute to CH's pathophysiology through other mechanisms, which requires further exploration of additional clock genes or regulatory factors.[41]

Chorong Han et al consider that the nitroglycerin (NTG) chronic headache paradigm is a useful model for studying migraine and chronic headache. Through this model, they found that NTG mice exhibit circadian rhythms in pain sensitivity. Following the knockout of *Per1* and *Per2*, the circadian rhythm of pain in the NTG model mice was abolished, resulting in elevated mechanical thresholds relative to wild-type NTG mice. Furthermore, RNA sequencing of trigeminal ganglia from NTG-headache model and control mice was performed every 4 h for 24 h, and the results revealed 466 genes that displayed circadian oscillations in the control group, including core clock genes and clock-regulated pain neurotransmitters. In the NTG group, they observed a profound circadian reprogramming of gene expression, as 331 of circadian genes in the control group lost rhythm and another 584 genes gained rhythm.[59]

Pain Management

Based on the current clinical applications of circadian rhythm research, this review summarizes them into two main treatment strategies. The first is chronotherapy, which aims to improve the effect and efficiency of treatment while reducing side effects by choosing a more suitable treatment time according to the diurnal changes of the disease. The second approach involves targeting clock genes as therapeutic targets, utilizing agonists or inhibitors of these genes as pharmacological agents, or employing traditional Chinese medicine techniques such as moxibustion to positively modulate the clock genes for therapeutic purposes (Table 2).

Chronotherapy for Analgesia

Considering the influence of circadian rhythms of pain, optimizing drug release timing through chronotherapy has emerged as a novel therapeutic strategy. RA characterized by the hallmark clinical symptoms of morning stiffness and afternoon relief was first investigated by J R de Andrade[60] in 1964, who observed that most patients experienced superior outcomes when administering prednisolone at night compared to taking the same doses during the day. Building upon this research, Nils Gunnar Arvidson[70] conducted a study in 1997 comparing the effects of administering prednisolone to RA patients at 2:00 am and 7:30 am. He found that IL-6 concentrations were reduced by 80% in the group receiving treatment at 2:00 am, accompanied by significant alleviation of pain symptoms; conversely, no notable changes were observed in IL-6 concentrations or symptoms among those treated at 7:30 am. Further animal experiments showed that Satoru Koyanagi et al found through liver cell and mice studies that continuous prednisolone administration during low endogenous cortisol specifically activates aberrant Per1 transcription in peripheral tissues, disrupting circadian rhythms. In contrast, continuous prednisone administration under high cortisol conditions did not significantly affect the rhythmicity of clock genes, nor did it affect the rhythms of locomotor activity and body temperature.[61] Since cortisol levels peak at night in humans, this may also explain why glucocorticoids administered in the evening exhibit better analgesic efficacy.

However, waking patients for medication administration at 2:00 am is impractical for clinical application and not conducive to widespread adoption. Consequently, modified-release formulations of prednisone have been developed for nighttime administration prior to sleep, allowing active drug release approximately four hours later (at around 2:00 am)

Table 2 Pain Management

Treatment Strategy	Specific Methods/ Drugs	Research Evidence and Key Findings	Advantages	References
Chronotherapy for Analgesia	**Prednisolone**	- Administration at 2:00am reduced IL-6 concentrations by 80% and alleviated pain symptoms - Administration when endogenous cortisol levels are high does not disrupt rhythm - Modified-release formulations developed for nighttime administration	Improves efficacy, reduces side effects; aligns with circadian rhythms.	[60,61]
	NSAIDs (eg, Indomethacin)	- Nighttime dosing showed superior analgesic efficacy and lower incidence of central nervous system side effects compared to morning dosing - Efficacy varied with administration timing in animal models (eg, midnight or onset of light cycle)	Effective with fewer side effects.	[62–64]
Clock genes-Based Biologics for Analgesia	**REV-ERBα agonists (eg, SR9009)**	- Activation of REV-ERBα suppressed LPS-induced inflammation, reducing IL-1β and IL-18 production - Alleviated acute inflammatory and neuropathic pain	Novel targeted therapy, high safety, validated in multiple models.	[65–67]
	Moxibustion	- Restored *Rev-erbα* mRNA rhythm and upregulated *Rev-erbα* to inhibit inflammatory factors in RA rats - Alleviated CFA-induced arthritic pain by enhancing BMAL1 and CLOCK expression	Traditional Chinese therapy with no side effects; modulates endogenous rhythms.	[68,69]

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to optimize therapeutic efficacy.[62] In addition to prednisolone, certain nonsteroidal anti-inflammatory drugs (NSAIDs), such as indomethacin, demonstrate superior analgesic efficacy when administered at night compared to morning dosing, while also exhibiting a lower incidence of central nervous system side effects.[63]

Animal studies have demonstrated that the efficacy of pain relief varies significantly depending on the timing of administration. In a murine model of chronic constriction injury (CCI), it was observed that the analgesic effects of CREB-miR and CRTC1-miR in alleviating neuropathic pain were more pronounced when administered at midnight compared to noon (with lights on at 0:00 am and off at 12:00 pm).[64] Similarly, in a kaolin-induced pain model in mice, indomethacin exhibited superior analgesic effects when given at 8:00am (with lights on at 7:00 am and off at 7:00 pm) compared to other time points.[65] Notably, drug administration coinciding with the onset of a 12-hour light cycle yielded better therapeutic outcomes than that aligned with a 12-hour dark cycle; this finding contrasted with human circadian rhythms, potentially due to inherent differences between species.

While chronotherapy shows potential in enhancing drug efficacy, it is also necessary to consider patient adherence to timed medication administration. Strictly following the medication schedule can be challenging for patients with poor adherence. Additionally, there are individual differences in circadian rhythms among patients, as each person has a unique sleep-wake cycle. Therefore, for different patients, personalized chronotherapeutic administration schedules should be developed, and optimized strategies for individualized drug delivery should be explored.

Clock Genes-Based Biologics for Analgesia

In addition to choosing optimal treatment timing on the circadian rhythm for enhancing analgesic effects, targeting clock genes represents a novel therapeutic strategy for pain relief. For example, SR9009, a small molecule agonist of REV-ERBα, has been shown by Huiling Hong et al to significantly suppress LPS-induced inflammation in vitro and in vivo through pharmacological activation of REV-ERBα;[66] SR9009 though BMAL1 inhibited NLRP3-mediated IL-1β and IL-18 production in macrophages, indicating that BMAL1 was indispensable in inhibiting IL-1β expression. Building on this foundation, Sangeet Makhija[71] further investigated that a single administration of REV-ERBα agonist was sufficient to mitigate the initial inflammatory response elicited by λ-carrageenan injections in Sprague-Dawley rats of acute inflammatory pain. Thus, it can be conclusively stated that REV-ERBα effectively alleviates inflammatory pain by inhibiting inflammatory processes in rats.

Notably, SR9009 exhibits high safety and specific targeting: it shows extremely low toxicity to normal cells, with no significant weight loss or tissue damage observed in mice following long-term administration. By exerting its effects through direct binding to REV-ERBα, SR9009 lays the foundation for clinical translation.[67] Furthermore, Norimitsu Morioka[72] also blocked the production of pronociceptive molecules (IL-1β, IL-6, and MMP-9) in LPS-treated cultured spinal astrocytes by utilizing SR9009, while validating the effective analgesic effects of intrathecal administration of SR9009 in mouse models of CFA-induced peripheral inflammatory pain, as well as in various mouse models of neuropathic pain such as PSNL, paclitaxel and streptozotocin induced neuropathic pain. Currently, other biological agents targeting clock genes, such as CRY agonists (eg, KL001),[68] have yet to be reported in relation to pain.

Apart from the agonists of clock genes, moxibustion can also regulate the clock genes to relieve pain. Moxibustion is a traditional Chinese medical therapy that involves burning dried mugwort on or near acupoints to stimulate meridians and treat diseases through thermal stimulation. It is widely employed in the treatment of RA, demonstrating significant efficacy in alleviating pain without adverse effects. Research into its molecular mechanisms indicates that its analgesic properties are closely linked to the regulation of clock genes. Wu X et al[69] demonstrated that *Rev-erbα* can inhibit the secretion of inflammatory factors, thereby mitigating inflammatory responses. In RA rat models, the circadian rhythm of *Rev-erbα* mRNA was lost; however, moxibustion recovered this rhythm. Moxibustion suppresses circulating levels of inflammatory factors by upregulating *Rev-erbα* expression across various tissues in RA rats, alleviating inflammation associated with rheumatoid arthritis. Additionally, Xinling He et al[73] found that chrono-moxibustion can treat RA in CFA-induced arthritic rats by enhancing the expression of BMAL1 and CLOCK to achieve analgesic outcomes.

Limitations and Discussion

There are still significant limitations in the research on circadian rhythms and pain. Firstly, current research techniques are unable to monitor the changes of each clock gene in real time in vivo, which requires sampling and detecting the clock genes in animal

tissue at different points of the day, and resulting in a huge workload for experiments. Therefore, the current research on the influence of circadian rhythm on pain focuses on the abnormal expression of clock genes rather than allorhythmia. Second, circadian rhythm disruption is substantially mediated by sleep disturbances, and such disruption can induce hyperalgesia and the development or exacerbation of spontaneous pain symptoms. Studies on the molecular mechanisms underlying pain induced by such disruption have primarily focused on opioid, monoaminergic, melatonin systems, etc,[74] with limited attention to clock genes disorders. Therefore, there is currently a lack of direct evidence to explain the pain caused by sleep disorders from the perspective of dysregulation of clock gene. Third, existing studies have not adequately focused on age-specific characteristics: the circadian rhythm system is immature in the pediatric population, while the elderly population exhibits declined clock gene expression and reduced melatonin secretion. However, current research primarily uses adult animals as models, failing to reveal age-related differences in pain rhythms and thus limiting the development of age-stratified treatment strategies.

Conclusion

As discussed above, circadian rhythms, as an important mechanism within organisms, are precisely regulated by clock genes and influence various physiological processes, including pain. Existing research has revealed the potential role of clock genes in the initiation and progression of pain, providing new insights into pain treatment. However, despite some progress, the specific mechanisms by which clock genes regulate pain are still not fully understood, and related research remains inadequate. We expect that there will be more research on circadian rhythms and pain in the future, providing more comprehensive solutions for pain management and treatment, and truly improving the quality of life for patients.

Data Sharing Statement

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Ethical Approval

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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