Heliyon 9 (2023) e15986

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Review article

Current role and future perspectives of electroacupuncture in circadian rhythm regulation

Min Yuan [a], Wei Lu [a], Ying Lan [b], Jiaen Yang [c], Jun Yin [a], Dong Wang [a,*]

[a] Department of Rehabilitation Medicine, Affiliated Hospital and Clinical Medical College of Chengdu University, Chengdu, China
[b] Department of Intensive Care Unit, Affiliated Hospital and Clinical Medical College of Chengdu University, Chengdu, China
[c] Department of TCM Rehabilitation Medicine, Affiliated Foshan Gaoming Hospital of Guangdong Medical University, Foshan, China

ARTICLE INFO

Keywords:
Electroacupuncture
Circadian rhythm
Time dependence
Diseases

ABSTRACT

In recent years, in-depth research on chronobiology has been conducted, and the circadian rhythm has become a new target for the treatment of diseases. Circadian rhythms are closely related to the normal physiological functions of organisms. Increasing evidence indicates that circadian rhythm disorders are the pathological basis of diseases such as sleep disorders, depression, cardiovascular diseases, and cancer. As an economical, safe, and effective treatment method, electroacupuncture has been widely used in clinical practice. In this paper, we summarize the current literature on electroacupuncture's regulation of circadian rhythm disorders and circadian clock genes. In addition, we briefly explore the optimization of electroacupuncture intervention programmes and the feasibility of implementing electroacupuncture intervention programmes at selected times in clinical practice. We conclude that electroacupuncture may have good application prospects in circadian rhythm regulation, but this conclusion needs to be confirmed by clinical trials.

1. Introduction

There has been ongoing effort to obtain a deep understanding of the physiologic formation of the circadian rhythm and how it plays a role in the body. Additionally, there is great interest in how circadian rhythm oscillation is determined by the circadian clock system. Circadian rhythm describes the endogenous oscillation of an approximately 24-h period associated with the daily rotation of the Earth and the light/dark cycle. This rhythm reflects the existence of a circadian clock in organisms. Additionally, the circadian clock coordinates time and physiological processes so that the internal environment of an organism can adapt to the external environment and respond to environmental changes [1]; this concept is consistent with the idea of "harmony between human and nature" in traditional Chinese medicine.

Circadian rhythms have a wide range of functions, regulating a variety of intracellular signalling pathways, such as cell proliferation, DNA damage repair and response, angiogenesis, metabolism, redox homeostasis, and inflammation and immune responses [2]. It plays a key role in controlling the physiological functions of almost all tissues and organs [3]. Therefore, the disturbance of circadian rhythm is closely related to diseases [4–7]. Under normal circumstances, humans wake up during the day and sleep at night, and the circadian rhythm is adapted to the external environment. However, when the circadian rhythm is affected by endogenous and/or exogenous factors, abnormalities in the circadian rhythm are induced, potentially leading to the occurrence of diseases. For

* Corresponding author.
E-mail address: wangdong@cdu.edu.cn (D. Wang).

https://doi.org/10.1016/j.heliyon.2023.e15986
Received 7 January 2023; Received in revised form 2 April 2023; Accepted 28 April 2023
Available online 2 May 2023

Table 1
Summarizes the existing studies on circadian rhythm regulation by electroacupuncture for different diseases, including insomnia, depression, hypertension, acute ischemic stroke, CFS, and liver cancer.

Author/year	Sample size	Study object	Stimulation parameter	Evaluation	Target disease	EA effects on circadian rhythm	Time dependence
Liu Zhen et al., 2016 [33]	120 (control/model/EA acupoint/EA non-acupoint: 30 rats in each group)	SD rats	Shenmai (BL62), Zhaohai (KI6)	EEG/EMG analyses and serum MT	Insomnia	Improve the circadian rhythm of MT	0:00
Yao H-J et al., 2014 [34]	24 (control/model/EA group: 8 rats in each group)	SD rats	Baihui (GV20), Yintang (GV29); qd/20 min, for 21 days; 2 Hz, the head of the rat was slightly shivering	Open-field experiment, temperature, and serum MT	Depression	Improve the circadian rhythm of temperature and MT	Not reported
Yang, Dianhui, 2010 [35]	60 (30 patients in each group, EA group: F: 13, average age: 40.4 ± 5.2 years/western medication group: F: 10, 41.7 ± 4.2 years	Young hypertension patients	Quchi (LI11), Taichong (LR3), qd/30min, for 14 days, 2 Hz/100 Hz, 10–20 mA	24-h dynamic BP, BP variability and day-night rhythm	Hypertension	Increase the number of patients with dipper hypertension, reduce non-dipper hypertension	Not reported
Xu Xin-yin et al., 2020 [36]	120 (normal/sham MCAO/MCAO model/sham EA/EA)	SD rats	Shenshu (BL23), Baihui (GV20), qd/15 min, for 3 days; 2 Hz, 0.2 ms pulse width, 1–2 mA	Neurological deficits; infarct size; ultrastructure; inflammatory cytokines; cell apoptosis; protein expression of Bax, bcl-2, caspase-3, Clock and Bmal1	Acute ischaemic stroke	Upregulate the expression of Clock and Bmal1	Not reported
Cheng Ci-song et al., 2010 [37]	40 (20 individuals in each group, healthy group: F: 18, average age: 37.10 ± 6.87 years/CFS group: F: 18, 34.35 ± 7.27 years	Healthy subjects and CFS patients	Shenshu (BL23), Zusanli (ST36), qd/20min, for 10 days, dense wave, intensity of stimulation was based on patient comfort	P3a and P3b latencies	CFS	Shift the latency acrophase of P3a and P3b forward	14:00
Hou Shuai et al., 2018 [38]	108 (control/model/EA group: according to 6 ZT, 6 rats in each group)	C57BL/6J rats	Ganshu (BL18), Zhiyang (GV9); qd/15 min, for 10 days; 2 Hz/15 Hz, 0.2 mA	Pathological changes in liver cells and the expression level of Per 1 and Per 2 mRNA in liver tissue	Liver cancer	Improve the amplitude of activity and advance the peak phase	ZT8 (15:00)

BP = blood pressure, CFS = chronic fatigue syndrome, EA = electroacupuncture, EEG = electroencephalograph, EMG = electromyography, F = female, MCAO = middle cerebral artery occlusion, MT = melatonin, SD = Sprague-Dawley, ZT = zeitgeber time.

example, changes in the light/dark cycle in an environment and/or genetic abnormalities damage the normal entrainment of the circadian rhythm system, resulting in chronic circadian rhythm sleep disorders (CRSDs) [8]. Circadian rhythm not only affects sleep but also causes or affects the development of other diseases. Studies have shown that circadian rhythm disorders are closely associated with diseases such as cancer [9–11], cardiovascular diseases [12,13], severe depression and bipolar disorder [14–16].

In addition, due to the circadian rhythm, many diseases exhibit different changes at different times of the day: many patients with nonseasonal depression show a regular daily symptom pattern, usually with more severe symptoms in the morning [17]; asthma symptoms are usually the most severe at night and early in the morning [18]; patients with rheumatoid arthritis have more obvious symptoms of joint stiffness and pain in the morning [19]; acute coronary syndrome or atrial fibrillation often occurs in the early morning [20]; and stroke incidence peaks in the morning, with a second peak the early evening [21]. Similarly, a meta-analysis showed that among 106 studies that compared at least 2 treatment regimens at different times, 75% of the studies found that for multiple diseases, the treatment effect depended on the time of drug administration [22]. This evidence indicates that time is a key dimension of effective treatment and that breakthroughs in the field of chronotherapy rely on a complete understanding of circadian rhythms [3].

Recently, studies on the treatment of diseases from the perspective of circadian rhythms have gradually increased, revealing numerous treatment methods according to differences in circadian rhythm-related diseases, studies have found that a ketogenic diet may change circadian rhythm gene expression and induce the rearrangement of metabolic gene expression, indicating that this dietary approach may improve obesity and metabolic pathology [23]. Studies have shown that glucocorticoids can affect the body's immune system by affecting the circadian rhythm [24]. Similarly, a number of studies have shown a close relationship between melatonin and circadian rhythm disorders [25]. Wang and colleagues proposed that the circadian rhythm of the gut microbiota plays a key role in host metabolism, physiology and health. These theories laid the foundation for the development of targeted chronotherapy involving the gut microbiota [26]. In addition, intermittent feeding, phototherapy, antidepressants, moxibustion, and acupuncture have all been shown to effect circadian rhythms and improve related diseases [27–30].

Electroacupuncture is a kind of acupuncture, which is a common treatment approach in traditional Chinese medicine and has been applied in many countries around the world. Electroacupuncture, as compared to acupuncture, employs electrical stimulation with varying frequencies and intensities, which can stimulate acupoints more effectively than twisting needles or other manual manipulation procedures. It compensates for the drawbacks of acupuncture's insufficient stimulation intensity and demonstrates greater efficacy in clinical practice. Studies have demonstrated the regulatory effect of electroacupuncture on the circadian rhythm. In traditional electroacupuncture theory, there is a medical-related mechanism of timely acupoint selection, supporting the above discussion. In this study, we summarize the current literature on the regulation of circadian rhythm disorders and circadian clock genes by electroacupuncture. In addition, we briefly discuss the optimization of electroacupuncture protocols and the feasibility of implementing electroacupuncture protocols at selected times in clinical practice.

2. Methods

In this article, the keywords "Electroacupuncture" or "EA" or "acupuncture" and "Circadian rhythm" or "Circadian clock" were used to identify all studies that investigated electroacupuncture and circadian rhythm. Relevant papers were retrieved from Google Scholar, PubMed, the China National Knowledge Infrastructure (CNKI) and the WanFang databases between January 1, 2012 and December 31, 2022. The search was restricted to English or Chinese language articles and included both randomized controlled trials and clinical trials. Eligibility evaluation was done by title and abstract reviews and when abstracts did not provide enough information, the full text of the paper was retrieved for evaluation. If data were found to duplicated and published more than once, the comprehensive study was chosen for inclusion in the review.

3. Effects of electroacupuncture on circadian rhythm in clinical diseases

Increasing evidence has shown that as a non-light zeitgeber time (ZT), electroacupuncture has a positive regulatory effect on the circadian rhythm [31]. However, the effect of electroacupuncture on the regulation of circadian rhythms is different due to temporal characteristics. For example, electroacupuncture promotes rhythm resynchronization in an advanced light-dark cycle-shifting environment but has a different or even opposite effect at different time points. Electroacupuncture was shown to have a significant promoting effect of rhythm resynchronization at 3 time points, ZT4, ZT8, and ZT12, no significant effect at ZT16 and ZT0, and might delay rhythm resynchronization at ZT20 [31]. Similarly, the results of a study by Liu showed that under the guidance of the light-dark cycle, the spontaneous activity and body temperature of rats exhibited obvious circadian rhythm changes. Acupuncture at different times of the day has different effects on spontaneous activity and circadian rhythms of body temperature. In addition to the influence of the median and amplitude of the circadian rhythm, electroacupuncture can also significantly affect the peak phase of the circadian rhythm. It can delay the peak phase of the circadian rhythm at the Mao period and advance the peak phase at the You period [32]. The following summarizes the existing studies on circadian rhythm regulation by electroacupuncture for different diseases (Table 1).

3.1. Effects on sleep disorders

Sleep and wakefulness are the most obvious circadian rhythms in mammals. The disruption of circadian rhythms can lead to chronic CRSDs [39]. Sleep disorders can impair physical health and mental function, such as increasing the incidence of obesity, cardiovascular disease, metabolic syndrome, and depression [8]. Although the currently approved drugs are effective, they are not satisfactory due to their side effects. For example, drugs such as chloral hydrate, barbiturates, and benzodiazepines may cause

excessive daytime sleepiness, poor drug tolerance, dependence and addiction. Increasing evidence shows that electroacupuncture can safely and effectively improve sleep disorders without side effects [40–42].

The mechanism by which electroacupuncture improves insomnia may be related to the regulation of the circadian rhythm of melatonin. Melatonin is one of the hormones secreted by the pineal gland. Its secretion exhibits a significant circadian rhythm. In the human body, melatonin secretion is inhibited during the day. It plays an important role in circadian rhythm maintenance and sleep regulation [43]. In a rat model of insomnia, melatonin rhythm was disrupted. Electroacupuncture can regulate and restore the rhythm of melatonin secretion in a rat model of insomnia, thus reducing wakefulness, increasing non-rapid eye movement sleep, reducing the duration of non-rapid eye movement short duration sleep and improving insomnia [33]. In terms of acupuncture points selection, the effects at “Shenmai (BL62)" and “Zhaohai (KI6)" (see schematic diagram of acupoint, Fig. 1) are more pronounced [33,44].

3.2. Effects on depression

Depression is a common clinical emotion-related psychiatric disease, and its clinical manifestations are low mood, pessimism, and cognitive and sleep disorders. Its pathogenesis is complex. Current studies on the treatment of depression with acupuncture mainly focus on neurobiochemistry (such as 5-hydroxytryptamine) and neuroendocrinology (inflammatory cytokines, such as IL-1, IL-6, and IL-18) [34]. In recent years, with advancements in chronobiology, circadian rhythm has become a hot spot in the study of the mechanism of electroacupuncture treatment of depression. Circadian rhythm disorders play important roles in the pathophysiology of depression [45,46]. Studies have shown that the incidence of depression is higher among young individuals with circadian rhythm disorders [47]. A study of 85 patients with bipolar disorder showed that changes in circadian rhythm were associated with depressive symptom severity, mood regulation disorders, and suicidal tendencies [48]. The study showed that compared with that of rats in the control group, the circadian rhythm of rats in the depression model group disappeared, the phase of the body temperature rhythm peak was advanced, the phase of the melatonin peak was delayed, and the rhythm amplitude was lower. In addition to electroacupuncture restoring circadian rhythm and increasing amplitude, the behaviour data for a post-electroacupuncture open-field test suggested better results for the treatment group than for the model group, indicating that electroacupuncture can improve depression by regulating the circadian rhythm [34,49]. Yuichi Esaki and colleagues also confirmed that a stable circadian rhythm is significantly associated with a reduction in the recurrence of depressive symptoms in patients with bipolar disorder [16].

3.3. Effects on cardiovascular diseases

Circadian rhythm is closely related to cardiovascular physiology and pathological function [20,50]. Heart rate, blood pressure and endothelial function exhibit rhythmic changes throughout the day [20]. Currently, although antihypertensive drugs are the first-line treatment for hypertension, compliance is poor, and thus, there is still a need for a safe, effective, and adjuvant treatment method that improves patient compliance. As a nondrug intervention, acupuncture can effectively control blood pressure [51,52]. The combination of acupuncture and drugs can improve clinical outcomes [53]. Blood pressure also has a circadian rhythm, exhibiting double peaks and one trough, with the first peak occurring in the morning after waking up and exercising, a second slightly higher peak occurring in the afternoon, and a trough occurring while sleeping [54]. The nocturnal decrease in blood pressure is part of the normal circadian rhythm. In hypertension patients, nocturnal blood pressure can significantly predict the prognosis of cardiovascular diseases, and the ratio of diurnal/nocturnal blood pressure can predict mortality [55]. Acupuncture can improve the daytime mean systolic blood pressure, daytime mean diastolic blood pressure, nighttime mean systolic blood pressure, and circadian rhythm of systolic blood pressure in patients with essential hypertension and increase the dipping rate [56,35]. Compared with dipping hypertension, non-dipping hypertension is more likely to cause damage to target organs, and the circadian rhythm of nondipping blood pressure is an important factor that aggravates cardiovascular damage.

The circadian rhythm of stroke incidence is closely related to the circadian rhythm of blood pressure. Regardless of the type of stroke, the circadian rhythms are generally similar; that is, there are two peaks of disease onset: in the morning and in the early evening [57]. In addition to the peak incidence of ischaemic stroke, there is also a trough, that is, the lowest incidence at midnight [58]. In

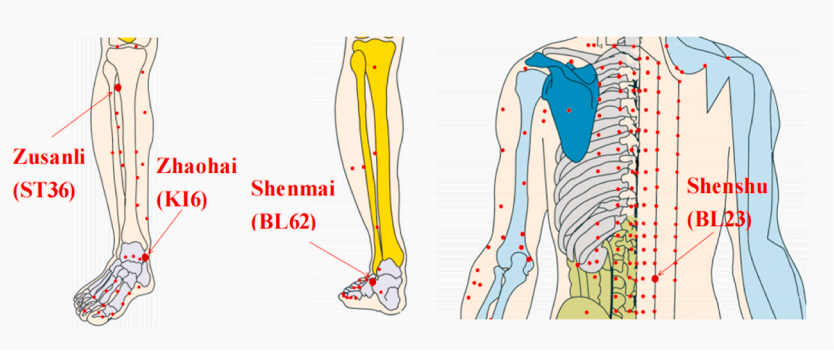

Fig. 1. Schematic diagram of acupoint “Shenshu (BL23)”, “Zusanli (ST36)”, “Zhaohai (KI6)”, “Shenmai (BL62)”.

addition to the circadian rhythm of incidence, severity also has a circadian rhythm. Compared with those at other time points, the infarct volume, brain swelling, nerve defects, and apoptotic cell death caused by ischaemic stroke at midnight (ZT18, 24:00) are milder [59]. Xu's study reported that electroacupuncture can regulate the expression of circadian clock gene proteins, reduce infarct size and neuronal apoptosis, and exert a neuroprotective effects [36].

3.4. Effects on fatigue

Chronic fatigue syndrome (CFS) manifests not only as chronic fatigue that lasts for a long period of time (more than 6 months) but also as decreased memory and attention [60]. The cause and pathological mechanism of the disease have not been determined. In recent years, with advancements in chronobiology, it has been found that circadian rhythm disorders may be one of the pathogenic mechanisms of CFS. Studies have shown that CFS patients have hypothalamic–pituitary–adrenal axis (HPAA) circadian rhythm disorders [61,62]. There is a distinct circadian rhythm in the latency of P3a and P3b in healthy adults. However, the circadian rhythms of both P3a and P3b latencies were shown to not be present in CFS patients, and the peak rhythms were significantly shifted backwards compared to those of the healthy group. Electroacupuncture treatment can shift the peak phase forward, restore the circadian rhythm of P3b latency, increase the amplitude and improve the daytime cognitive agility of patients [37]. Zhu's study also showed that electroacupuncture at "Shenshu (BL23)" and "Zusanli (ST36)" (see schematic diagram of acupoint, Fig. 1) significantly improved the somatic functional status, psychological functional status, social functional status and general health of CFS patients [63].

3.5. Effect on cancer

Circadian rhythm dysregulation is a potential triggering factor and/or pathological outcome of cancer [3]. The International Agency for Research on Cancer (IAC) listed "shift-work that involves circadian disruption" as potentially carcinogenic based on limited evidence in humans and sufficient evidence in experimental animals [64]. There is evidence that compared with those who do not work night shifts, the risk of prostate cancer is higher in night shift workers, and the risk increases with the extension of night shift hours [65]. The disruption in the circadian rhythm is not only related to the incidence of cancer [4], but also the accelerated progression of cancer [66].

Circadian rhythm genes participate in the biological pathways of cancer, such as cell proliferation and apoptosis, by controlling the expression of tumour suppressor genes, cell cycle genes, and genes encoding caspases and transcription factors [66]. A study by Hadadi and colleagues showed that changing the normal circadian rhythm significantly increased the proliferation and lung metastasis of breast cancer cells [67]. Studies have shown that electroacupuncture can regulate the disordered circadian rhythm of cancer. In a mouse model of liver cancer, compared with that in the blank group, the activity amplitude in model mice was significantly lower, and the activity peak lagged. Electroacupuncture was shown to boost the active amplitude and was most effective at ZT8 (15:00); furthermore, it was shown to shift the lagged peak phase forward [38].

An increasing number of studies have demonstrated that electroacupuncture can regulate circadian rhythm, but the internal mechanism of how electroacupuncture regulates circadian rhythm is still not completely clear, and whether the regulatory effect of electroacupuncture has a therapeutic effect on diseases remains to be investigated.

4. Mechanism

The circadian rhythm exists in almost all organisms and is an endogenous rhythm that is driven by the circadian clock in organisms and adapted to the natural environment. The circadian clock is composed of 3 parts: input (zeitgeber, such as light), the clock system, and output. The clock system is the core of the circadian clock. The suprachiasmatic nucleus (SCN) in the brain is the central clock and is responsible for integrating perceived external light signals to transmit information to the peripheral clock. In addition, the clock system determines the molecular mechanisms of circadian rhythms, that is a transcriptional translational feedback loop (TTFL).

Clock and Bmal1 form a heterodimer, Clock/Bmal1, that binds to the E-box region to activate the transcription of Per and Cry genes. These genes then form a Per/Cry complex, which puts the body to sleep. When Per/Cry reaches a certain concentration, it inhibits Clock/Bmal1 to promote wakefulness, forming a feedback loop [68]. In addition, the circadian clock nuclear receptors REV-ERB and ROR are important components of the body's circadian clock system and play important roles in maintaining biological rhythms. The activation and inhibition of Clock and Bmal1 genes occur through REV-ERBs (inhibition) and RORs (activation). These two nuclear receptors are also transcriptionally activated by Clock and Bmal1 [69].

Studies have shown that acupuncture exerts a therapeutic effect by regulating the expression of Clock/Bmal1. At the molecular level, Clock/Bmal1 is a core component of the circadian clock, and the clock/Bmal1 heterodimer drives the expression of other circadian clock genes [5]. Bmal1 activity is a necessary condition for the generation of circadian rhythms in gene expression and behaviour [70]. Studies have shown that acupuncture upregulates the expression levels of the circadian clock genes Clock and Bmal1 in the hypothalamic ventrolateral preoptic nucleus (VLPO) and SCN regions of rats with insomnia, thereby improving insomnia [71]. Circadian rhythm dysregulation may lead to DNA damage and the increased expression of oxidative stress and inflammation-related gene products, thereby triggering ischemia-induced cell death [72]. Electroacupuncture can have a neuroprotective effect on neuronal apoptosis after ischaemic stroke by increasing the protein expression of Clock and Bmal1 [36]. Similarly, the results of Wang and his colleagues confirmed that both Clock and Bmal1 played an important role in regulating the pathological process of cerebral ischaemic injury. They pointed that early acupuncture can inhibit inflammation caused by cerebral ischemia more effectively by upregulation of Clock and Bmal1 proteins [73]. In addition, Per1 and Per2 are important rhythmic factors, and their deletion can lead to rhythm

disorders. Studies have shown that the disruption of Per1 or Per2 genes causes the circadian rhythm system to become unstable [74]. Guo's study showed that acupuncture upregulates the expression of Per1 and Per2 mRNA, promotes an increase in the Per/Cry complex, reduces the amount of activity during the rest period, and improves sleep in rats [44]. Furthermore, in mice with liver cancer, electroacupuncture significantly downregulated the relative expression levels of Per 1 and Per 2 mRNA, and Per and Cry synergistically reduced the inhibition of the negative feedback regulation of Clock/Bmal1, thus activating the restoration of circadian rhythms [75]. Acupuncture can regulate the circadian rhythm by upregulating or downregulating circadian clock genes. However, the underlying mechanisms are still unclear, and a great deal of further high-quality research is needed to fully elucidate the mechanisms. For example, regarding the upregulation of Clock and Bmal1 expression, the downstream pathways through which insomnia and neuronal protection are achieved have not been clearly elucidated. In addition, studies have reported that Bmal1 and Per2 regulate the expression of vascular endothelial growth factor (VEGF), thereby playing important roles in angiogenesis [76]. Can this finding be extended to the mechanism by which electroacupuncture regulates the circadian rhythm of cardiovascular diseases? The mechanism by which acupuncture regulates circadian rhythms has multitarget and multidirectional characteristics. In addition to the regulation of clock genes, the mechanisms may involve humoral factors, the autonomic nervous system, and metabolic factors, which may act as messengers to synchronize disrupted clocks in the body and obtain a balanced biological rhythm [69]. Fig. 2 summarizes the available literature on the internal mechanism by which electroacupuncture regulates the circadian rhythm.

5. Future perspectives

With advancements in chronobiological research, circadian rhythm has become a novel target for the treatment of diseases. An increasing number of studies have confirmed that as an economical, safe, effective, and convenient treatment method, electroacupuncture exerts regulatory effects on the circadian rhythm. However, different treatment times and different stimulation parameters affect electroacupuncture effectiveness and reliability. Next, we introduce factors related to optimizing experimental designs.

Because of the characteristics of circadian rhythms, the effectiveness of electroacupuncture treatment showed strong time dependence, and some studies investigated specific time protocols [32,37,38,75]. However, these studies used different zeitgeber times to implement the intervention. Some used zeitgeber time 6 [38,75], some used zeitgeber time 4 [32,37], and some studies did not mention zeitgeber time [34,35,36]. Because different diseases have rhythmic differences, future studies should use zeitgeber time to evaluate the impact of electroacupuncture on the circadian rhythms of diseases at different times to maximize the effect of electroacupuncture.

Regarding the setting of stimulation parameters, no consensus has been reached, and different acupuncture points, stimulation frequencies, and current intensities have been used in studies. Different acupuncture points can be used for different diseases. Although the specific treatment regimens vary from person to person, in the treatment of the same types of diseases, the main acupoints should be standardized, and secondary acupoints should be selected on the basis of individual differences. This approach should be considered in future studies. Second, regarding stimulation frequency, most studies used a fixed intensity of 2 Hz, and some studies used patient

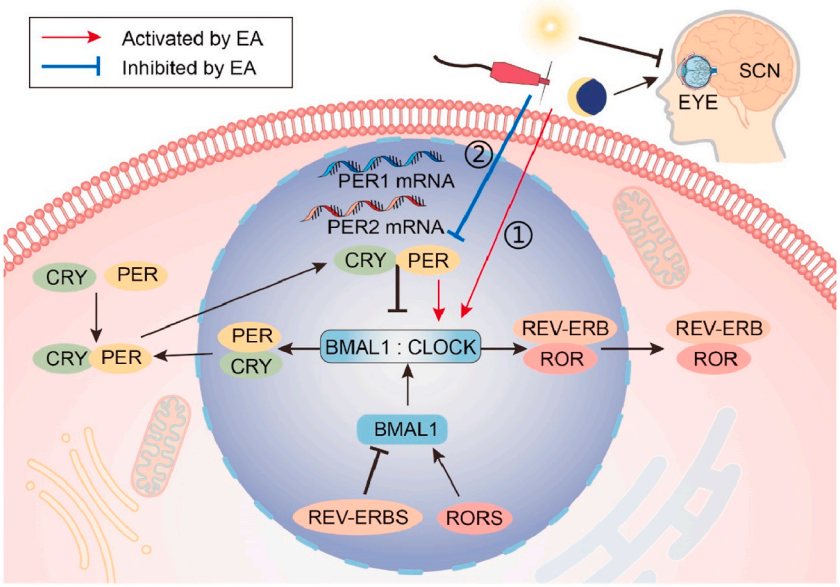

Fig. 2. The mechanism of electroacupuncture regulating circadian rhythm. Electroacupuncture, as a non-light zeitgeist, can ① improve sleep by upregulating the expressions of Clock and Bmal1 genes. ② In a mouse model of liver cancer, electroacupuncture down-regulates the expression of Per1 and Per2 mRNA, reduces the production of Per/Cry complex, then reduces the inhibition of Clock/Bmal1, and thus activates the expression of circadian rhythm genes.

tolerance as the standard. No study has demonstrated whether electroacupuncture at different frequencies has different effects on circadian rhythm regulation. In general, the stimulation parameters for electroacupuncture should be continuously optimized in future studies.

In addition, most studies chose to use a model group or sham electroacupuncture group as the control, and thus, the level of evidence provided by the study results must be improved. In future research protocols, clock knockout rats or rats treated with candidate drug molecules, such as KS15 (CRYs inhibitor), can be used as control groups; in KS15models, Per2 and REV-ERBα expression is increased and Bmal1 mRNA expression is decreased [77], thus potentially improving the level of evidence and improving the reliability of the results.

In most relevant studies, the regulation of clock and Bmal1 genes and of melatonin by electroacupuncture has been investigated, followed by the regulation of Per1 and Per2. However, it is still not clear through what pathway electroacupuncture initiates these regulatory effects. More studies are needed to reveal the in-depth mechanism and the regulatory role of more clock genes and establish more reliable biomarkers. It may be difficult to quickly capture the response of circadian clock genes to electroacupuncture, but it may be possible to obtain gene expression response times after electroacupuncture using high-throughput techniques.

Most experiments have been performed using animals such as rats, and there are differences in physiological circadian rhythms between animals and humans; for example, rats are more active at night. Can animal-based studies be extended to humans? Further verification is needed. In addition, the feasibility of electroacupuncture regimens to regulate circadian rhythms needs to be examined because the clinical application of electroacupuncture based on different time points has challenges involving cost and inconvenience. For example, acupuncture treatment times may depend on the needs of each patient, in the early morning, patient cooperation may be an issue; also are there enough medical personnel to complete large number of treatments early in the morning or at night?

6. Conclusion

Although the phenomenon of circadian rhythms was noticed very long ago, molecular characterization did not begin until the 1960s. Currently, there are few studies on circadian rhythm regulation by electroacupuncture, with animal experiments predominating. Therefore, applying research results to the clinic safely and effectively has been challenging. In future studies, the following 3 points should be considered to determine the effectiveness and safety of electroacupuncture in regulating circadian rhythms. First, the level of evidence in studies must improve. The effectiveness and safety of electroacupuncture in regulating the circadian rhythm of diseases should be verified using randomized controlled trials. Existing studies have all shown that electroacupuncture can effectively regulate circadian rhythms; however, the internal mechanisms are still not fully elucidated, and more high-quality studies are needed to reveal and verify the mechanisms. This can be achieved through the use of gene knockout mice, establishment of reliable biomarkers and/or the use of high-throughput technologies. Second, the experimental schemes among studies are quite different and need to be continuously optimized and standardized. Although there are individual differences in patients, the experimental protocols for each disease should be roughly standardized, for example, experimental procedure, main selected acupoint points, frequency of electroacupuncture, and length of treatment, and then, adjustments should be made based on individual patient differences. This may help to verify the beneficial effect of electroacupuncture in regulating circadian rhythms. Third, studies are needed to verify whether there is a difference in the effect of timed electroacupuncture and untimed therapy. In general, electroacupuncture may have good application prospects in regulating circadian rhythm, but clinical trials are needed to support the results of initial studies.

Funding

This work was supported by the Project of the Science and Technology Department in Sichuan province (Grant No. 2022YFS0403), the Scientific Research Project of Sichuan Province Health Commission (Grant No. 21PJ125), Sichuan Medical Youth Innovation Research Project (Q21031) and Affiliated hospital of Chengdu University Innovation Team Project (CDFYCX202202).

Author contribution statement

All authors listed have significantly contributed to the development and the writing of this article.

Data availability statement

Data included in article/supp. material/referenced in article.

Additional information

No additional information is available for this paper.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] A.R. Neves, et al., Circadian rhythm and disease: relationship, new insights, and future perspectives, J. Cell. Physiol. (2022).
[2] F. Halberg, Physiologic 24-hour periodicity: general and procedural considerations with reference to the adrenal cycle, Int. Z. Vitaminforsch. Beih. 10 (1959) 225–296.
[3] F. Fagiani, et al., Molecular regulations of circadian rhythm and implications for physiology and diseases, Signal Transduct. Targeted Ther. 7 (1) (2022) 41.
[4] E.A. Yu, D.R. Weaver, Disrupting the circadian clock: gene-specific effects on aging, cancer, and other phenotypes, Aging (Albany NY) 3 (5) (2011) 479–493.
[5] M.E. Young, M.S. Bray, Potential role for peripheral circadian clock dyssynchrony in the pathogenesis of cardiovascular dysfunction, Sleep Med. 8 (6) (2007) 656–667.
[6] S. Panda, Circadian physiology of metabolism, Science 354 (6315) (2016) 1008–1015.
[7] Y. Leng, et al., Association between circadian rhythms and neurodegenerative diseases, Lancet Neurol. 18 (3) (2019) 307–318.
[8] C. Liu, et al., Circadian rhythm sleep disorders: genetics, mechanisms, and adverse effects on health, Front. Genet. 13 (2022), 875342.
[9] L.B. Samuelsson, et al., Sleep and circadian disruption and incident breast cancer risk: an evidence-based and theoretical review, Neurosci. Biobehav. Rev. 84 (2018) 35–48.
[10] T. Papagiannakopoulos, et al., Circadian rhythm disruption promotes lung tumorigenesis, Cell Metabol. 24 (2) (2016) 324–331.
[11] Z. Wang, et al., Circadian clock genes promote glioma progression by affecting tumour immune infiltration and tumour cell proliferation, Cell Prolif. 54 (3) (2021), e12988.
[12] T.A. Martino, et al., Circadian rhythm disorganization produces profound cardiovascular and renal disease in hamsters, Am. J. Physiol. Regul. Integr. Comp. Physiol. 294 (5) (2008) R1675–R1683.
[13] S.S. Thosar, M.P. Butler, S.A. Shea, Role of the circadian system in cardiovascular disease, J. Clin. Invest. 128 (6) (2018) 2157–2167.
[14] H.K. Mishra, et al., Circadian rhythms in bipolar disorder patient-derived neurons predict lithium response: preliminary studies, Mol. Psychiatr. 26 (7) (2021) 3383–3394.
[15] Y. Takaesu, et al., Circadian rhythm sleep-wake disorders as predictors for bipolar disorder in patients with remitted mood disorders, J. Affect. Disord. 220 (2017) 57–61.
[16] Y. Esaki, et al., Association between circadian activity rhythms and mood episode relapse in bipolar disorder: a 12-month prospective cohort study, Transl. Psychiatry 11 (1) (2021) 525.
[17] D. Riemann, et al., Sleep, insomnia, and depression, Neuropsychopharmacology 45 (1) (2020) 74–89.
[18] K. Krakowiak, H.J. Durrington, The role of the body clock in asthma and COPD: implication for treatment, Pulm Ther 4 (1) (2018) 29–43.
[19] W. Grassi, et al., The clinical features of rheumatoid arthritis, Eur. J. Radiol. 27 (Suppl 1) (1998) S18–S24.
[20] N. Takeda, K. Maemura, Circadian clock and cardiovascular disease, J. Cardiol. 57 (3) (2011) 249–256.
[21] R. Manfredini, et al., Circadian variation in stroke onset: identical temporal pattern in ischemic and hemorrhagic events, Chronobiol. Int. 22 (3) (2005) 417–453.
[22] M.D. Ruben, et al., Dosing time matters, Science 365 (6453) (2019) 547–549.
[23] E. Gangitano, et al., Chronobiology and metabolism: is ketogenic diet able to influence circadian rhythm? Front. Neurosci. 15 (2021), 756970.
[24] A. Shimba, A. Ejima, K. Ikuta, Pleiotropic effects of glucocorticoids on the immune system in circadian rhythm and stress, Front. Immunol. 12 (2021), 706951.
[25] C. Vasey, J. McBride, K. Penta, Circadian rhythm dysregulation and restoration: the role of melatonin, Nutrients 13 (10) (2021).
[26] H. Wang, H. Zhang, Y. Su, New insights into the diurnal rhythmicity of gut microbiota and its crosstalk with host circadian rhythm, Animals (Basel) 12 (13) (2022).
[27] H.M. Kim, et al., Can acupuncture affect the circadian rhythm of blood pressure? A randomized, double-blind, controlled trial, J. Alternative Compl. Med. 18 (10) (2012) 918–923.
[28] X. Wu, et al., Moxibustion benignantly regulates circadian rhythm of REV-ERBα in RA rats, Am J Transl Res 12 (5) (2020) 1459–1468.
[29] I.W.K. Kouw, L.K. Heilbronn, A.R.H. van Zanten, Intermittent feeding and circadian rhythm in critical illness, Curr. Opin. Crit. Care 28 (4) (2022) 381–388.
[30] C.K. Mahendra, et al., Cosmeceutical therapy: engaging the repercussions of UVR photoaging on the skin's circadian rhythm, Int. J. Mol. Sci. 23 (5) (2022).
[31] D. Cai, et al., Research on phase characteristic of acupuncture on circadian rhythm disturbance due to advanced light/dark cycle, China Journal of Traditional Chinese Medicine and Pharmacy (4) (2011) 691–694.
[32] X.G. Liu, et al., Effects of acupuncture at different periods on circadian rhythms of locomotor activity and core body temperature in hamsters, Zhongguo Zhen Jiu 25 (6) (2005) 417–419.
[33] Z. Liu, et al., Influence of electroacupuncture on regulating the circadian rhythm of sleep-wake and melatonin in rats with insomnia, China Journal of Traditional Chinese Medicine and Pharmacy (9) (2016) 3695–3699.
[34] H.-J. Yao, et al., Effects of electroacupuncture on circadian rhythm of temperature and melatonin in depression rats model induced by chronic stress, Zhongguo Zhen jiu= Chinese Acupuncture & Moxibustion 34 (7) (2014) 685–689.
[35] D.H. Yang, Effect of electroacupuncture on Quchi (LI 11) and Taichong (LR 3) on blood pressure variability in young patients with hypertension, Zhongguo Zhen Jiu 30 (7) (2010) 547–550.
[36] X.Y. Xu, et al., Effect of electroacupuncture on neurological deficit and activity of clock and Bmal1 in cerebral ischemic rats, Curr Med Sci 40 (6) (2020) 1128–1136.
[37] C.S. Cheng, et al., Effect of electroacupuncture at Shenshu (BL 23) and Zusanli (ST 36) on the event-related potentials of chronic fatigue syndrome, Zhongguo Zhen Jiu 30 (4) (2010) 309–312.
[38] S. Hou, et al., Effect of electroacupuncture at different time on circadian rhythm and SCN epigenetic modification in mice with hepatocellular carcinoma, Zhongguo Zhen jiu= Chinese Acupuncture & Moxibustion 38 (8) (2018) 864–870.
[39] Y. Dagan, Circadian rhythm sleep disorders (CRSD), Sleep Med. Rev. 6 (1) (2002) 45–54.
[40] B. Lee, et al., Efficacy and safety of electroacupuncture for insomnia disorder: a multicenter, randomized, assessor-blinded, controlled trial, Nat. Sci. Sleep 12 (2020) 1145–1159.
[41] S.P. Kim, et al., Electroacupuncture for insomnia disorder: study protocol for a randomized controlled trial, Trials 18 (1) (2017) 177.
[42] J.W. Ruan, et al., Electroacupuncture treatment of chronic insomniacs, Chin Med J (Engl) 122 (23) (2009) 2869–2873.
[43] Z. Xie, et al., A review of sleep disorders and melatonin, Neurol. Res. 39 (6) (2017) 559–565.
[44] B.J. Guo, et al., Effect of acupuncture at points in heel vessel for circadian clock genes of period 1 and period 2 mRNAs in the suprachiasmatic nucleus in insomnia rats, Zhen Ci Yan Jiu 42 (6) (2017) 507–509.
[45] A. Germain, D.J. Kupfer, Circadian rhythm disturbances in depression, Hum. Psychopharmacol. 23 (7) (2008) 571–585.
[46] S.K. Satyanarayanan, et al., Circadian rhythm and melatonin in the treatment of depression, Curr. Pharmaceut. Des. 24 (22) (2018) 2549–2555.
[47] C. Nguyen, et al., In vivo molecular chronotyping, circadian misalignment, and high rates of depression in young adults, J. Affect. Disord. 250 (2019) 425–431.
[48] L. Palagini, et al., Chronobiological dis-rhythmicity is related to emotion dysregulation and suicidality in depressive bipolar II disorder with mixed features, Psychiatr. Res. 271 (2019) 272–278.
[49] X. Hong, et al., Effects of acupuncture on circadian rhythm of CORT and mPer1/mPer2 genes expression on diabetes mellitus rats with depression, Liaoning Journal of Traditional Chinese Medicine (3) (2018) 483–486.
[50] M.S. Bray, et al., Disruption of the circadian clock within the cardiomyocyte influences myocardial contractile function, metabolism, and gene expression, Am. J. Physiol. Heart Circ. Physiol. 294 (2) (2008) H1036–H1047.
[51] F.A. Flachskampf, et al., Randomized trial of acupuncture to lower blood pressure, Circulation 115 (24) (2007) 3121–3129.
[52] Y. Liu, et al., Acupuncture lowers blood pressure in mild hypertension patients: a randomized, controlled, assessor-blinded pilot trial, Compl. Ther. Med. 23 (5) (2015) 658–665.

[53] J. Yang, et al., Acupuncture for hypertension, Cochrane Database Syst. Rev. 11 (11) (2018) Cd008821.
[54] M.H. Smolensky, R.C. Hermida, F. Portaluppi, Circadian mechanisms of 24-hour blood pressure regulation and patterning, Sleep Med. Rev. 33 (2017) 4–16.
[55] R.H. Fagard, et al., Daytime and nighttime blood pressure as predictors of death and cause-specific cardiovascular events in hypertension, Hypertension 51 (1) (2008) 55–61.
[56] Y. Lei, et al., Effects of acupuncture on circadian rhythm of blood pressure in patients with essential hypertension, Zhongguo Zhen Jiu 37 (11) (2017) 1157–1161.
[57] D.M. Fodor, M.M. Marta, L. Perju-Dumbravă, Implications of circadian rhythm in stroke occurrence: certainties and possibilities, Brain Sci. 11 (7) (2021).
[58] F.K. Pardiwalla, M.E. Yeolekar, S.K. Bakshi, Circadian rhythm in acute stroke, J. Assoc. Phys. India 41 (4) (1993) 203–204.
[59] M.C. Beker, et al., Time-of-Day dependent neuronal injury after ischemic stroke: implication of circadian clock transcriptional factor Bmal1 and survival kinase AKT, Mol. Neurobiol. 55 (3) (2018) 2565–2576.
[60] J.R. Yancey, S.M. Thomas, Chronic fatigue syndrome: diagnosis and treatment, Am. Fam. Physician 86 (8) (2012) 741–746.
[61] A. Di Giorgio, et al., 24-hour pituitary and adrenal hormone profiles in chronic fatigue syndrome, Psychosom. Med. 67 (3) (2005) 433–440.
[62] D. Racciatti, et al., Chronic fatigue syndrome: circadian rhythm and hypothalamic-pituitary-adrenal (HPA) axis impairment, Int. J. Immunopathol. Pharmacol. 14 (1) (2001) 11–15.
[63] Y.-h. Zhu, et al., A randomized controlled trial of electroacupuncture for chronic fatigue syndrome, Shanghai J. Tradit. Chin. Med. (10) (2008) 48–50.
[64] T. Kantermann, T. Roenneberg, Is light-at-night a health risk factor or a health risk predictor? Chronobiol. Int. 26 (6) (2009) 1069–1074.
[65] K. Papantoniou, et al., Night shift work, chronotype and prostate cancer risk in the MCC-Spain case-control study, Int. J. Cancer 137 (5) (2015) 1147–1157.
[66] L. Fu, C.C. Lee, The circadian clock: pacemaker and tumour suppressor, Nat. Rev. Cancer 3 (5) (2003) 350–361.
[67] E. Hadadi, et al., Chronic circadian disruption modulates breast cancer stemness and immune microenvironment to drive metastasis in mice, Nat. Commun. 11 (1) (2020) 3193.
[68] J.A. Mohawk, C.B. Green, J.S. Takahashi, Central and peripheral circadian clocks in mammals, Annu. Rev. Neurosci. 35 (2012) 445–462.
[69] U. Albrecht, Molecular connections between circadian clocks and mood-related behaviors, J. Mol. Biol. 432 (12) (2020) 3714–3721.
[70] R.V. Khapre, et al., Circadian clock protein BMAL1 regulates cellular senescence in vivo, Cell Cycle 10 (23) (2011) 4162–4169.
[71] X.R. Wei, et al., Effect of acupuncture stimulation of different acupoint combinations on sleep and expression of circadian clock and bmal 1 genes in hypothalamus of insomnia rats, Zhen Ci Yan Jiu 42 (5) (2017) 429–433.
[72] A. Rami, J. Fekadu, O. Rawashdeh, The hippocampal autophagic machinery is depressed in the absence of the circadian clock protein PER1 that may lead to vulnerability during cerebral ischemia, Curr. Neurovascular Res. 14 (3) (2017) 207–214.
[73] Q. Wang, et al., Effects of acupuncture on circadian Clock and Bmal1 in rats with acute cerebral ischemia, Chinese Journal of Physical Medicine and Rehabilitation (9) (2020) 839–842.
[74] K. Bae, et al., Differential functions of mPer1, mPer2, and mPer3 in the SCN circadian clock, Neuron 30 (2) (2001) 525–536.
[75] S. Hou, et al., Electroacupuncture intervention regulates circadian rhythms by down-regulating per gene expression in hypothalamic suprachiasmatic nucleus of hepatocellular carcinoma mice, Zhen Ci Yan Jiu 43 (10) (2018) 632–639.
[76] L.D. Jensen, et al., Opposing effects of circadian clock genes bmal1 and period2 in regulation of VEGF-dependent angiogenesis in developing zebrafish, Cell Rep. 2 (2) (2012) 231–241.
[77] S.K. Chun, et al., A synthetic cryptochrome inhibitor induces anti-proliferative effects and increases chemosensitivity in human breast cancer cells, Biochem. Biophys. Res. Commun. 467 (2) (2015) 441–446.