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REVIEW

Interactions between remote ischemic conditioning and post-stroke sleep regulation

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Abstract **Sleep disturbances are common in patients with stroke, and sleep quality has a critical role in the onset and outcome of stroke. Poor sleep exacerbates neurological injury, impedes nerve regeneration, and elicits serious complications. Thus, exploring a therapy suitable for patients with stroke and sleep disturbances is imperative. As a multi-targeted nonpharmacological intervention, remote ischemic conditioning can reduce the ischemic size of the brain, improve the functional outcome of stroke, and increase sleep duration. Preclinical/clinical evidence showed that this method can inhibit the inflammatory response, mediate the signal transductions of adenosine, activate the efferents of the vagal nerve, and reset the circadian clocks, all of which are involved in sleep regulation. In particular, cytokines tumor necrosis factor α (TNFα) and adenosine are sleep factors, and electrical vagal nerve stimulation can improve insomnia. On the basis of the common mechanisms of remote ischemic conditioning and sleep regulation, a causal relationship was proposed between remote ischemic conditioning and post-stroke sleep quality.**

Keywords remote ischemic conditioning; sleep regulation; stroke

Introduction

Stroke is a common disease worldwide with prevalence and 1-year incidence rates of 1115/100 000 and 246.8/100 000 in China, respectively [1]. This condition has been the leading cause of death and disability with over RMB 40 billion yuan related annual expenses. Thus, improving the outcomes of stroke is of great importance. Sleep quality is one of the most important prognostic factors related to stroke (e.g., age, gender, and comorbidity).

Sleep is a naturally complicated phenomenon critical for physiologic activity, recovery, life quality. Good sleep is beneficial for plasticity, regeneration, and repairment, and poor sleep exacerbates energy failure, excitotoxicity, inflammation, and complications [2]. Stroke per se has detrimental effects on sleep, and over 50% of patients with ischemic stroke have complaints of insomnia [3]. Thus, improvements on the sleep quality of patients with stroke has drawn attention. Current strategies for insomnia in post-stroke have their limitations. Hypnotic drugs promote sleep quickly but tend to induce sleep-disordered breathing, cognition impairment, and weakness [4]. Cognitive-behavioral treatment is effective and safe but is hindered by its slow effects and the lack of professional therapists [5]. Other strategies, such as transcranial magnetic stimulation, require specific equipment and particular individuals. Therefore, exploring a therapy suitable for patients with stroke and sleep disturbances is imperative.

Remote ischemic conditioning (RIC) may be a good choice. This endogenous, multi-targeted nonpharmacological intervention exerts protective effects on the brain and heart by inducing brief, non-lethal ischemia/reperfusion injury of extremities [6]. Given its non-invasiveness and easy feasibility, RIC has been an attractive therapy for cardiovascular and cerebrovascular patients. Its core mechanisms are neuronal signal transfer (e.g., vagus nerve), humoral factors (e.g., adenosine), and immunoregulation (e.g., cytokine interleukin-10) [7], all of which are involved in sleep regulation. For example, vagus nerve activation induces sleep, and adenosine and interleukin-10 (IL-10) are sleep factors.

Owing to its protective effects on the brain and its

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multiple mechanisms shared with sleep regulation, RIC has the potential to be a novel therapy for patients with stroke and sleep disturbances. In this review, the underlying interrelations among sleep, stroke, and RIC were first explored. Preclinical/clinical evidence that link sleep to RIC was also presented. Finally, several mechanisms of RIC regulatory effects on sleep were discussed, such as inflammatory response, adenosine signaling system, autonomic nervous system, and circadian clocks.

Sleep disturbances and stroke

The sleep–wake cycle is generated by the mutual competition of sleep-promoting neurons and wake-promoting neurons and is affected by various factors, such as brain functions, genes, humoral/neural signals, behavior, psychological beliefs, and ambient environment, most of which are abnormal in post-stroke. According to a recent systematic review [3], stroke is frequently accompanied by sleep disturbances, such as insomnia, sleep-disordered breathing, circadian rhythm dysfunctions, and sleep-related movements disorders. Pace *et al*. [8] investigated the features of sleep architecture in acute ischemic stroke and found markedly decreased rapid eye movement (REM) sleep in rodent animals and unfavorable outcomes correlated to decreased REM sleep amounts and prolonged REM latency in patients with stroke. However, different studies reported variations in other characteristics of post-stroke sleep, such as sleep depth, sleep efficiency or sleep architecture. In general, lesion locations, brain edema, severity, or comorbidities of stroke directly influence sleep quality [8–10].

Sleep quality is also critical for the onset and recovery of stroke. On the one hand, sleep disturbances are risk factors for the onset of stroke. Sleep deprivation facilitates atherogenesis and endothelial dysfunction [11], leading to a high incidence and recurrence rate of stroke. McAlpine's study [12] showed that mice subjected to sleep fragmentation produced many Ly-6Chi monocytes and developed large atherosclerotic plaques, suggesting that sufficient sleep protects the artery against atherosclerosis. On the other hand, sleep quality correlates to outcomes of stroke. Sleep deprivation after ischemic stroke results in extended infarct size and poor outcomes with reduced axonal sprouting and increased damaged cells [13–15]. Interventions aimed at improving sleep can promote stroke recovery. In their clinical trials, Nguyen *et al*. [16] found that cognitive-behavioral therapy improved sleep quality in patients with stroke accompanied by decreased neurologic deficits. In rodent experiments, Hodor *et al*. [17] found that sleep-promoting drugs, which increase non-rapid eye movement (NREM) sleep, can improve the performance of stroke rats in single pellet reaching test and the neurogenesis of the peri-infarct region.

Therefore, stroke is a strong predisposing factor for sleep disturbances, and sleep quality has dual-directional effects on stroke prevention and recovery. For patients with stroke, a method that possesses neuroprotection and sleep improvement must be explored.

Remote ischemic conditioning and stroke

Preconditioning is a potentially detrimental stimulus that is close to but below the irreversible injury threshold and could increase organ resistance to subsequent harmful stimuli [18]. This approach is regarded as a hormetic-like biphasic dose response that protects cells from noxious stimulations by inducing a subtoxic increase of oxidative stress, inflammation, and other signals [19]. For example, a subtoxic level of mitochondrial reactive oxygen species (ROS) activates the adaptive stress response pathways of ischemic preconditioning [20], which in turn reduces the excessive production of mitochondrial ROS [21] by affecting the expression of heat-shock proteins [22] or nuclear factor erythroid 2-related factor [23]. Neurons, which are exposed to low levels of oxidative stress, can be resistant to a subsequent lethal oxidative stress [24].

RIC is a typical form of preconditioning: applying multiple, brief episodes of non-lethal ischemia/reperfusion injury in limbs can protect remote organs (e.g., brain and heart) from prolonged lethal ischemia and reperfusion. This method was first reported by Przklenk, then corroborated in multiple, diverse models [25], and is currently widely applied in patients with cardiovascular and cerebrovascular disease. RIC has two windows of protection. The first window occurs immediately after short durations of ischemia/reperfusion, and the second window of protection re-appears at 12–24 h after the brief episodes of ischemia/reperfusion and is maintained for 72–96 h [21]. Cheng *et al*. [26] reported that in mice with cerebral ischemia, RIC could attenuate hemispheric swelling and brain atrophy and reduce motor deficits and lesion size. Another study suggested [27] that RIC augmented cerebral perfusion and decreased memory impairment in chronic cerebral hypoperfusion model mouse. In their clinical trials, Zhao *et al*. [28] showed that RIC can reduce ischemic brain injury secondary to carotid artery stenting. Meng *et al*. [29] reported that RIC effectively increases cerebral perfusion and decreases the recurrence risk of stroke in patients with intracranial arterial stenosis. Furthermore, RIC improves depression in patients after stroke and slows down cognition impairment [30]. Therefore, this strategy exerts beneficial effects on brain functions, mood, and memory.

Although the systematic protections of RIC have been

described in preclinical and clinical observations, its molecular mechanisms are unclear. RIC elicits a cascade of downstream effects by activating the neuro-humoral-immune response. The neural pathways include peripheral sensory nerves, efferent vagal nerves, and spleen, which are indispensable for the protective effects of RIC. Ganglion blockers, cervical vagotomy, or femoral nerve transection can abolish RIC neuroprotection, and vagus nerve stimulation can be resistant to ischemia/reperfusion injury in the brain [7]. Humoral factors consist of triggers (e.g., adenosine, acetylcholine, and ROS), cytosolic mediators (e.g., protein kinase C–endothelial nitric oxide synthase–protein kinase G pathway, reperfusion injury salvage kinase pathway, and survival activating factor enhancement pathway), and intracellular effectors (e.g., nucleus and mitochondria) [21]. RIC neuroprotection can be transferred to another animal by transporting blood derivatives. The immune regulation includes the preactivation of the immune system and anti-inflammatory response. Liu *et al*. [31] reported that RIC can reverse the reduction in B cell population after stroke. These mechanisms work together to protect multiple organs of the body.

RIC exerts endogenous protections by neural pathways, humoral factors, and immune regulations, all of which are important components of sleep regulation. Hence, this strategy is feasible for patients with stroke and sleep disturbances.

Correlations between remote ischemic conditioning and sleep regulation

Although the correlations among sleep, stroke, and RIC have been described, the causal link between RIC and sleep remains unknown. In this work, direct/indirect evidences that RIC plays a role in sleep regulation were discussed (Fig. 1).

An animal experiment showed that RIC can alter the sleep phenotype. Brager and his colleagues [32] monitored the sleep electroencephalogram of mice before and after RIC (brief limb ischemia for 10 min in the hind legs of mice followed by reperfusion for 10 min, 2 cycles) and found that the mice's sleep increased 2.4 h in one day. This additional sleep was mainly composed of NREM sleep. In a further experiment, they disturbed the excess sleep induced by RIC and consequently abolished the RIC neuroprotection against ischemia/reperfusion (I/R) injury. This study indicates that RIC increases sleep duration and additional sleep is essential to RIC protective effects. Despite the limited clinical studies, patients with cerebrovascular or cardiovascular diseases and healthy volunteers often report that RIC makes them sleep better and provides them improved sleep satisfaction and less fragmented sleep. Moreover, RIC even immediately induces sleep after the treatment for some patients.

Melatonin is involved in sleep regulation and RIC neuroprotection and is mainly secreted by the pineal gland and is suppressed after stroke [33]. This substance can shorten sleep-onset latency, improve sleep quality [34], and protect the brain/heart from I/R injury [35]. Experimental studies showed that melatonin administered before lethal I/R injury exhibited protective effects for the brain, which is similar to ischemic preconditioning. Feng *et al*. [36] revealed that pre-ischemia melatonin treatment reduced cerebral infarct size and brain edema and generated good outcomes. Furthermore, melatonin is required in RIC protective effects. In their rodent study [37] that investigated whether melatonin mediates RIC cardioprotection, researchers found that the administration of melatonin could decrease the infarct size of the heart in wild-type rats. This effect is similar to RIC. However, in rats with pinealectomy, RIC decreased the infarct size slightly, whereas RIC plus exogenous melatonin substantially reduced the infarct size. These results indicate that melatonin is indispensable for RIC. However, clinical trials failed to confirm that exogenous melatonin supplements can reduce myocardial infarction size. The results of MARIA trial showed that melatonin even worsens adverse remodeling after myocardial infarction [38]. Although we cannot conclude its influence on the concentration or effects of melatonin, RIC may be involved in the signal transductions of melatonin.

As two classic patterns of preconditioning, RIC and sleep deprivation preconditioning partially share mechanisms, such as the activation of Toll-like receptors, temperature regulation, and antioxidant activity [39]. Using microarray analysis, Pace *et al*. [40] found that sleep deprivation preconditioning reprograms signal responses in ischemic brain tissues, thus inhibiting cell division and inflammatory response. Konstantinov *et al*. [41] also found that RIC downregulated the expression levels of proinflammatory genes. RIC and sleep deprivation both alleviate ischemic damage and improve neurological performances. Hsu *et al*. [42] found that sleep deprivation prior to cerebral ischemia could attenuate brain damage and glial reactions. Moldovan *et al*. [43] reported that total sleep deprivation for 6 h limited the neurological deficits induced by reversible middle cerebral artery occlusion. Moreover, the neuroprotection of sleep deprivation preconditioning depends on sleep-rebound (the significantly increased quantity of slow wave activity and paradoxical sleep in post-stroke), which contributes to axonal sprouting, neuroplasticity, and neurogenesis [44]. RIC tolerance against I/R injury also relies on the extra sleep induced by RIC in preischemic stroke [32]. Therefore, its role in sleep regulation may be similar to sleep deprivation preconditioning.

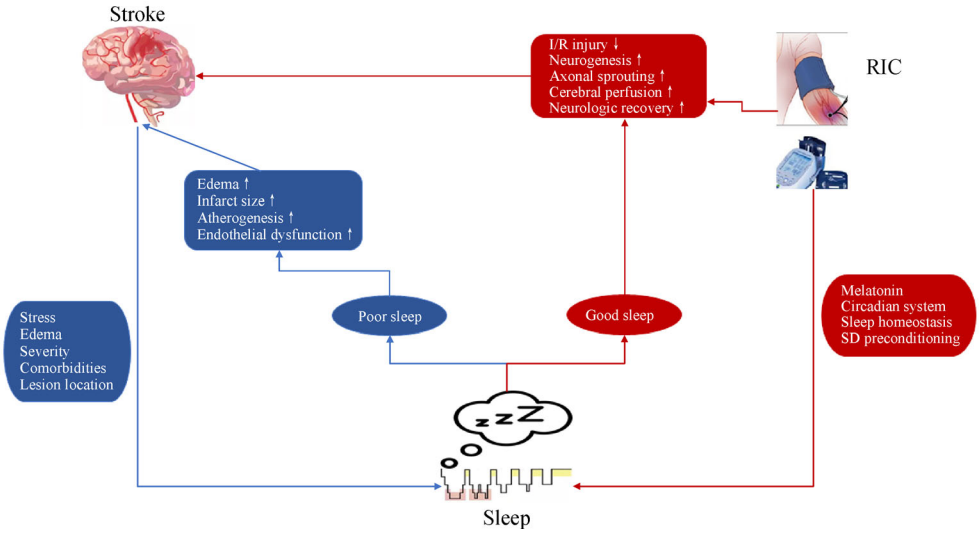

Fig. 1 Evidence that links stroke, remote ischemic conditioning (RIC) and sleep. Stroke and sleep disturbances have mutually adverse effects. Stress, brain edema, severity, comorbidities, and lesion location that are resulted from stroke induce sleep disturbances, while poor sleep facilitates atherogenesis, endothelial dysfunction, extended edema, and infarct region. RIC and good sleep have similarly neuroprotective effects, such as reducing ischemia/reperfusion (I/R) injury, increasing neurogenesis, axonal sprouting, and cerebral perfusion. Furthermore, RIC involves in sleep regulation, by impacting melatonin, sleep homeostasis, and circadian system, as well as by the shared mechanisms of sleep deprivation (SD) preconditioning.

Mechanisms of sleep regulation by remote ischemic conditioning

Several common mechanisms were found between sleep regulation and RIC, including neural feedback, humoral signal transfer, and inflammation [7,45]. Therefore, RIC might mediate sleep homeostasis via these mechanisms (Fig. 2).

Inflammatory response

The inflammatory response has a causal role in sleep quality and duration. Physiologically, cytokines such as interleukin-1 (IL-1) and tumor necrosis factor α (TNF-α) are sleep factors that accumulate gradually in wakefulness; sleep occurs when their concentrations meet the threshold value [46]. The concentrations of TNF-α and IL-1β increase substantially before the initiation of sleep [47]. Pathologically, different concentrations of pro-inflammatory cytokines have conflicting effects on sleep. The mild inflammatory reaction triggered by low doses of endotoxin would enhance NREM sleep [48], whereas the proinflammatory response induced by severe infection would aggravate sleep fragmentation [49]. Anti-inflammatory cytokines such as IL-4 and IL-10 can also promote sleep. Thus, any intervention that can regulate the immune response can directly or indirectly influence sleep quality and duration.

Given that immunoregulation is a primary pathway of its endogenous mechanisms, RIC may improve sleep quality via modulating inflammatory response. At first, RIC can induce the pre-activation of the immune system prior to the stroke, which is supported by clinical studies. Castillo *et al.* [50] found that transient ischemic attack, the natural ischemic preconditioning in humans, predicts a good functional outcome for subsequent acute stroke accompanied by mildly elevated concentrations of TNF-α in serum. Gedik *et al.* [51] also reported that RIC applied prior to ischemic injury increased the IL-1α concentration in the arterial blood samples of patients with cardiopathy. Given that the moderate elevation of TNF-α or IL-1 induces slow wave sleep, RIC may regulate sleep by preactivating the immune system. Animal experiments showed that RIC affects peripheral immune cell populations and inhibits the excessive proinflammation after stroke. Liu *et al.* [31] found that RIC rescued the decline in B cell population and ameliorated the reduction of $CD3^+CD8^+$ T cells and $CD3^+/CD161a^+$ NKT cells after stroke, thus further affecting the secretion of cytokines. TNF-α, IL-6, interferon-γ (IFN-γ), and IL-2 rapidly exceed the pathological threshold in post-stroke, thereby aggravating the excitatory neural toxicity and further interrupting sleep continuity [52–54]. Most studies suggested that RIC can alleviate the overwhelming inflammatory response induced by I/R injury via decreasing the release of IL-6, IL-1β, and TNF-α [52]. Finally, RIC increases the concentrations of anti-inflammatory cytokines, which is beneficial for sleep quality in post-stroke. Cai *et al.* [55]

reported that RIC induces late protection against myocardial I/R injury by increasing IL-10 expression in the remote muscle, followed by the release of IL-10 into the circulation. Therefore, RIC could improve sleep continuity by suppressing the hyperactivation of the inflammatory response after ischemic stroke.

RIC may facilitate the normalization of sleep patterns by balancing pro-inflammation and anti-inflammation.

Adenosine and adenosine receptor

Adenosine is an autacoid associated with energy demand and supply [56] and involved in sleep regulation. The concentration of extracellular adenosine regulates the waxing and waning of sleep propensity. In the subarachnoid space, extracellular adenosine activates A1 receptor (A1R) in the basal forebrain and tuberomammillary nucleus to inhibit arousal and activates neurons in the ventrolateral preoptic nucleus via coupling to A2a receptor to promote sleep. Therefore, adenosine and its receptors are critical in sleep regulation [57].

Animal experiments revealed that adenosine is an indispensable feed-back mediator for ischemic conditioning. First, adenosine infusion in dogs mimics the neuroprotection of ischemic preconditioning [58], and adenosine preconditioning exhibits the same metabolic features as RIC [59]. Second, adenosine deaminase can abolish the protective effects of ischemic preconditioning [60]. Finally, preconditioned parenchyma can release more adenosine compared with that in the control group [61], though this strategy was considered controversial in another experiment. All these observations indicate that adenosine is required in the endogenous mechanisms of RIC, which may promote sleep via the signal transductions of adenosine.

Adenosine A1R is downstream of adenosine signaling and a key component of preconditioning. As a classic form of preconditioning, sleep deprivation preconditioning protects the brain from ischemia/reperfusion (I/R) injury by increasing recovery sleep, which is correlated to the availability of A1R [62]. Bjorness *et al*. [63] reported that in A1R knocknout (KO) mice, slow wave sleep (SWS) could normally occur in the natural sleep pattern, but no compensatory SWS of recovery sleep occurs after sleep deprivation. A1R plays a key role in RIC effects. The infusion of adenosine A1R selective agonists can delay the brain's tolerance to I/R injury [64] and can even substitute for ischemic preconditioning [65]. Meanwhile, the blockade of adenosine receptors can attenuate the protective effects of ischemic preconditioning [66]. On the basis of A1R functions, RIC may be involved in sleep regulation.

Endogenous adenosine signaling is one of the underlying mechanisms of RIC. This approach can regulate sleep propensity by affecting the signal cascade of adenosine and the subsequent activation of A1R.

Autonomic nervous system

The autonomic nervous system has featured activations in different sleep stages. Sympathetic neural activity increases during REM sleep or wakefulness and decreases during NREM sleep, and vagal activity exhibits the opposite. For RIC protective effects, the autonomic neural activity is also indispensable. For example, bilateral cervical vagotomy can abrogate RIC neuroprotection, and electrical vagal nerve stimulation attenuates I/R injury [67]. Therefore, sympathetic–vagal balance is critical for sleep homeostasis and RIC protective effects.

RIC may attenuate sleep disorders by suppressing sympathetic activity. Sleep deprivation or insomnia induces the continuous activation of the sympathetic nerve system (SNS) and increases the levels of noradrenaline and adrenaline [68,69]. As a result, the percentage of wakefulness and REM sleep increases during the night, accompanied by sleep fragmentation and impaired recovery sleep [70,71]. Hence, reducing SNS activity could improve sleep quality. Ischemic stroke triggers SNS activation. In the acute phase, increased sympathetic outflows intensify inflammatory responses in ischemic tissues [72]. In the subacute or chronic phase, the persistent activation of SNS promotes chronic atherosclerosis by facilitating monocyte recruitment [73]. RIC can alleviate inflammation and atherosclerosis and may suppress SNS activity by stimulating nitric oxide production or activating K_{ATP} channels [74,75]. Tsutsui's study [76] showed that sympathetic activation, which is triggered by ischemia, could be attenuated by RIC. All these results suggest that RIC can improve sleep fragmentation by decreasing SNS activation.

RIC may improve sleep quality by activating efferent vagal nerves. Different from SNS, vagal activity has a dynamic role in NREM sleep. Reduced vagal activity prior to sleep initiation leads to SWS-loss, daytime sleepiness, and fatigue [77]. In a clinical pilot study, increased vagal nerve efferents induced by electrical stimulation could mitigate the insomnia symptoms of patients with stroke who show a decreased connectivity in the default mode network [78]. Thus, increasing the vagal activity can improve sleep quality. In rodent experiments, vagal nerve stimulation (VNS) in preischemia can mimic ischemic preconditioning's cardioprotection by activating muscarinic acetylcholine receptors and the intracellular phosphatidylinositol 3-kinase/serine-threonine kinase protein kinase pathway; meanwhile, VNS in reperfusion would simulate ischemic postconditioning by activating α7 nicotinic acetylcholine receptors and the Janus kinase 2 intracellular pathway [79]. Vagal nerve activities can attenuate reactive oxygen species formation, apoptosis, and inflammatory responses [80]. The vagal nerve is required for RIC effects, and cervical vagotomy, selective genetic targeting, or splenic denervation can abolish RIC

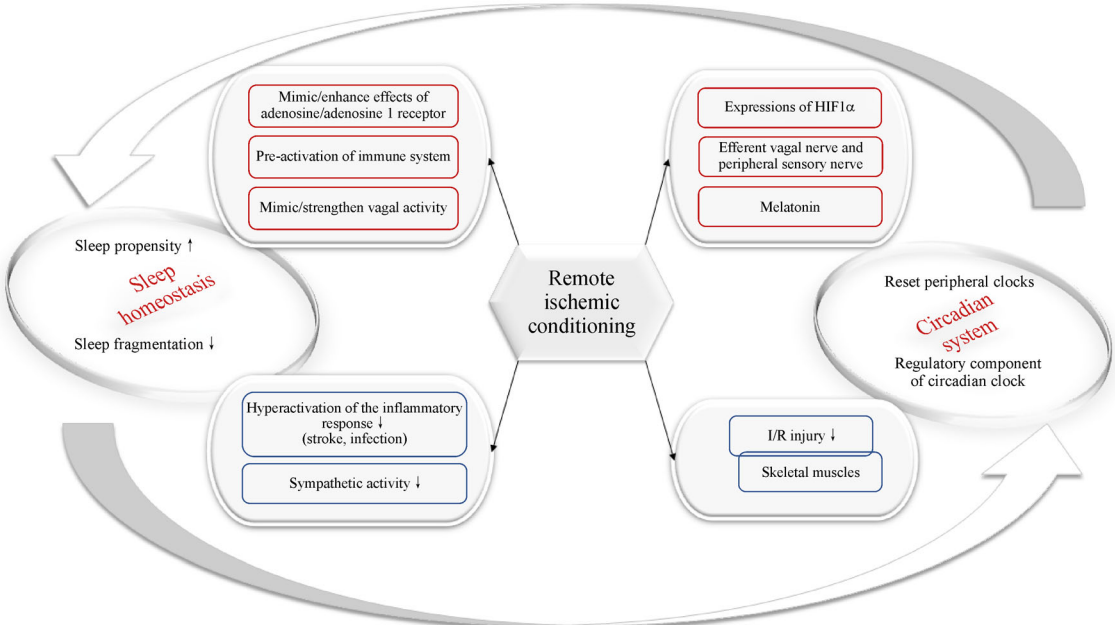

Fig. 2 Putative pathways linking remote ischemic conditioning to sleep regulation (sleep homeostasis and circadian system). RIC increases sleep propensity by the pre-activating immune system, mimicking/strengthening the effects of the adenosine system and vagal activity. It reduces sleep fragmentation by inhibiting the hyperactivation of inflammatory response and sympathetic activity. In addition, RIC plays a regulatory role in the circadian system, through increasing HIF1α, balancing neural activities, and decreasing ischemia/reperfusion (I/R) injury.

protections for the brain or heart [81].

In summary, RIC can modulate the activity of the autonomic nervous system by inhibiting the sympathetic activity and the activation of vagal activity. This approach can improve sleep continuity and depth by maintaining the sympathetic–vagal balance.

Circadian rhythm and circadian clocks

The circadian rhythm is driven by circadian clocks and is a multioscillatory network [82]. The molecular clock machinery contains coupled transcription–translation feedback loops with positive components (Bmal1 and Clock) and negative regulators (Per, Cry, and Rev-erbα) [83]. The master clock synchronizes internal rhythms with the environment and controls rhythms, timing, duration, and functions of the sleep–wake cycle. Peripheral clocks modulate the circadian rhythm and functions of organs/tissues and are involved in the sleep phenotype. Ehlen *et al*. [84] found that the mice with global knockout of Bmal1 and those with Bmal1 only expressed in the brain exhibited similar sleep disturbance, whereas Bmal1 only expressed in the skeletal muscle could rescue the sleep phenotype. In another experiment, the mice with local deletion of Bmal1 in the skeletal muscle had abnormal sleep patterns, and those with overexpression of Bmal1 only in the skeletal muscle were highly resistant to sleep loss. Thus, both clocks could change the sleep–wake pattern.

Circadian clocks are critical to 24 h variations of physiologic/pathological processes. For example, blood pressure, heart rate, and severity of ischemic events vary with time-of-day [85,86]. Conversely, circadian clocks are entrained by multiple factors. The master clock is genetically controlled and entrained by photic cues. Peripheral clocks are orchestrated by the master clock, temperature, hormones, and other non-photic cues (e.g., food intake, exercise, neural activity, and metabolites) [87,88]. RIC's endogenous mechanisms are involved in neural feedback, humoral transmitters, and immunoregulation; thus, this process might interact with circadian clocks. First, RIC may reset circadian clocks by inducing HIF1α. The heterozygous deficiency for HIF1α can abrogate the protection of ischemic preconditioning [89], which in turn can promote HIF1α expression in the brain, heart, and skeletal muscles [90,91]. Therefore, HIF1α has an ambivalent role in ischemic preconditioning, which indicates a threshold phenomenon. HIF1α attenuates mitochondrial ROS formation during hypoxia and is also a pre-requisite for mitochondrial ROS formation to initiate the protection by ischemic preconditioning [92]. HIF1α is also a regulatory component of BMAL1 and CLOCK [93,94]. Adamovich *et al*. [95] revealed that physiologic oxygen rhythms reset circadian clocks in a HIF1α-

dependent manner, and HIF1α knockdown would distinctly blunt the expression of Cry1/2, Rorα, and Per2. RIC could also regulate the activities of the vagus, sympathetic, and somatic nerves [96], and peripheral clocks are entrained by multiple neural signals [97]. On the basis of these observations, RIC could entrain circadian clocks. RIC may also reverse the altered circadian clocks in ischemic tissues. Ischemic damage can rapidly alter the expression levels of core clock genes and attenuate their circadian oscillations of ischemic tissues [98]. Moreover, I/R injury at zeitgeber time 18 increases the levels of circadian clock proteins (i.e., Per1, Clock, and Bmal1), with the smallest infarct size observed within 24 h [99]. Given that RIC can decrease ischemic lesions and increase neuronal survivals and blood supply [100,101], its ischemic protection may reverse circadian clocks' expression. Therefore, RIC could reset circadian clocks.

In summary, RIC shows the potential to reset circadian clocks and thereby regulates the sleep–wake cycle.

Conclusions

This work proposes a causal relationship between RIC and sleep, that is, RIC has the potential to regulate sleep. The underlying mechanisms of these sleep-promoting effects refer to immune response, humoral transmitters, neural activity, and circadian clocks. However, corroborative evidence is scarce, and research on post-stroke sleep disturbances is in its infancy. Sleep disorders, especially insomnia, are common in post-stroke and have detrimental influences on functional outcomes, but only a few interventions for sleep disturbances are tailored for patients with stroke. On the basis of its neuroprotection and sleep-improving effects, RIC may be a promising method for mitigating post-stroke sleep disturbances. In the future, a well-designed clinical research will be conducted to validate RIC's role in post-stroke sleep regulation. Additional experimental studies are also needed to explore the underlying mechanisms of RIC involvement in sleep regulation.

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Compliance with ethics guidelines

Xian Wang and Xunming Ji declare that they have no conflict of interest. This manuscript is a review article and does not involve a research protocol requiring approval by the relevant institutional review board or ethics committee.

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