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REVIEW

Electroacupuncture: A New Approach for Improved Postoperative Sleep Quality After General Anesthesia

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Abstract: General anesthesia produces a state of drug-induced unconsciousness that is controlled by the extent and duration of administered agents. Whether inhalation or intravenous in formulation, such agents may interfere with normal sleep–wake cycles, impairing postoperative sleep quality and creating complications. Electroacupuncture is a new approach widely applied in clinical practice during recent years. This particular technology helps regulate neurotransmitter concentrations in the brain, lowering norepinephrine and dopamine levels to improve sleep quality. It also alleviates surgical pain that degrades postoperative sleep quality after general anesthesia by downregulating immune activity (SP, NK-1, and COX-1) and upregulating serotonin receptor (5-HT1AR, 5-HT2AR) and endocannabinoid expression levels. However, large-scale, multicenter studies are still needed to determine the optimal duration, frequency, and timing of electroacupuncture for such use.

Keywords: general anesthesia, sleep quality, acupoints, electroacupuncture

Introduction

General anesthesia is an independent risk factor for circadian rhythm desynchronization, which subsequently alters the structure and quality of postoperative sleep.[1,2] Resultant changes in sleep quality include insomnia, hypersomnia, parasomnia, and sleep-related breathing disorders. Affected patients may demonstrate polysomnographic evidence of severe sleep deprivation or sleep fragmentation, as well as a lowering/loss of slow-wave sleep (SWS) and rapid eye movement (REM) sleep.[3,4] They may also report diminished sleep time, more episodic awakening, reduced sleep quality, and frequent nightmares.[5] Disturbances of this sort increase the incidence of postoperative complications, including postoperative fatigue, severe anxiety and depression, cardiovascular events, and pain sensitivity.[6,7] Long-term use of drugs to treat sleep disorders may lead to addiction and truncation, so their clinical utility is limited.[8]

Acupuncture has been a mainstay of Chinese health care for at least 2500 years, calling for the insertion of fine needles at specific acupoints. Bodily balance is thereby achieved and physiologic functions restored, without impacting natural sleep–wake cycles.[9] Acupuncture may actually improve sleep quality by increasing serotonin and aminobutyric acid levels, reducing glutamate levels via stimulatory means,[10,11] and eliciting sedative effects that preempt the use of hypnotics.[12]

Electroacupuncture is a new method of acupuncture that has gained wide clinical acceptance in recent years. It involves the provocation and adjustment of

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meridians and collaterals, applying micropulse current (akin to human bioelectricity) at specific acupoints for desired sensations. Electroacupuncture has been invoked for a variety clinical symptoms, including primary insomnia. The mechanisms entailed are fundamentally safe and effective for this purpose, capable of promoting quality sleep through direct autonomic nervous manipulation.[13] The present discussion addresses changes in sleep quality following general anesthesia, as well as mechanisms by which electroacupuncture improves quality of sleep and mitigates complications postoperatively.

Changes in Sleep Quality After General Anesthesia

Natural Sleep Pathway and Sleep Mechanisms Under General Anesthesia

In humans, the spontaneous sleep–wake cycle is a recursive organization involving two distinctive states, namely nonREM (NREM) and REM sleep. NREM sleep is further divisible into stages N1, N2, and N3, the latter being SWS. REM sleep accounts for 20–25% of total sleep in adults.[14] Various nerve centers, neurotransmitters, and endogenous sleep- or wake-related substances are involved in and seemingly drive the sleep–wake cycle.[15] The ventrolateral preoptic nucleus (VLPO) of the hypothalamus, a key area for sleep promotion, is chiefly composed of GABAergic neurons. The VLPO promotes sleep by inhibiting GABA synapses in the basal forebrain, hypothalamus, and brain stem,[16] whereas the nodal papillary nucleus and locus coeruleus are pivotal in driving cortical excitability and sobriety via norepinephrine release, their fibers coursing through the ascending reticular system. Ultimately, the sleep-arousal transition is achieved through active and rhythmic central nervous system (CNS) regulation.[17]

General anesthesia produces drug-induced states of unconsciousness. Such states are nonphysiologic and are not readily subject to environmental flux. They differ from natural sleep and are largely controlled by the extent and the duration of administered anesthetics. Given the array of agent-specific clinical differences, general anesthesia is hardly a singular phenomenon, instead representing an aggregate of the following discrete clinical endpoints: hypnosis (unawareness of one's environment), analgesia (lack of pain sensitivity), amnesia (loss of memory), and immobility after surgical stimulation.[18] Recent studies have discovered some commonality of mechanisms regulating general anesthesia and sleep.[7,19] There are behavioral similarities between sleep and anesthesia that may be linked to intracellular GABA levels within the brain. Bjornstrom and Eintrei have reported that GABA is involved in negatively regulating neuronal activity (eg, sleep), and most general anesthetics are known to be GABA agonists.[20] General anesthetics such as propofol and thiopental sodium induce sedation, hypnotization, and disappearance of consciousness by enhancing GABA neuronal activity in the VLPO and inhibiting nodal papillary nuclei and locus coeruleus.[21–23]

Effects of Various General Anesthetics on Postoperative Sleep Quality

Both inhalation and intravenous agents used as general anesthetics may interfere with normal sleep–wake cycles, causing melatonin disorders and affecting circadian clock genes, including period (*PER*), cryptochromes (*CRY), CLOCK*, and *BMAL1*, situated within suprachiasmatic nucleus.[24,25] Exposure to volatile general anesthetics, such as sevoflurane, isoflurane, and halothane, may cause short-term sleep disturbances and fragmentation. Use of isoflurane anesthesia during abdominal surgery seems to suppress SWS and nearly eliminate REM sleep on the first postoperative night, although this gradually abates, surpassing preoperative levels and intensifying.[26] Sevoflurane inhalation may induce REM sleep deficits, delayed REM sleep recovery, and decreased latency to REM sleep, without affecting wakefulness or nonREM sleep.[27]

Melatonin is an important neuroendocrine hormone that maintains the circadian rhythm and regulates sleep–wake cycles.[28] Cronin et al have shown that inhalation anesthesia delivered for gynecologic surgical procedures reduces nocturnal melatonin levels on the first (vs second or third) postoperative night, returning to baseline levels after the third night.[29] In adults undergoing cardiac surgery, intravenous anesthesia also seems to lower melatonin secretion on the night after its use.[30] Depending on perioperative concentration, secretion rhythm, and peak secretion, such changes may trigger sleep-wake cycle disorders, postoperative delirium, or cognitive dysfunction.[28,31-33]

Consequences of Changes in Sleep Quality After General Anesthesia

General anesthesia is known to diminish postoperative sleep quality. Structural and quality disturbances in postoperative sleep consequently heighten the incidence of postoperative complications (eg, delirium,[34] cognitive impairment,[35] cardiovascular adverse events,[36,37] immune hypofunction, etc).

Impact of Altered Sleep Quality on Cognition and Memory

Diminished postoperative sleep quality may incite inflammation, which bears a relation with hippocampal-dependent memory impairment and disturbed cognition.[38–40] Outcomes of a study by Gögenur et al have indicated a higher prevalence of sleep disturbance and more pronounced physiologic stress may figure prominently in the development of postoperative cognitive impairment by patients submitting to major abdominal surgery.[41] A normal sleep pattern is important for intact cognitive abilities. Even brief sleep pattern disturbances or voids of REM sleep during first or second postoperative night may contribute to early postoperative cognitive decline.[42]

Certain inflammatory mediators have been implicated in sleep and cognitive disturbances during the postoperative period. Kapsimalis et al have attributed impaired sleep and cognitive function to postsurgical cytokines (IL-1, IL-6) released in response to inflammatory stress.[43] Sleep deprivation after sevoflurane inhalation may also boost hippocampal expression of inflammatory factors IL-1β and IL-6. Reduced REM and SWS and increased fatigue have been produced by administering IL-6,[44] and increases in IL-6 concentration have been shown to degrade cognitive function.[45] It appears that increased IL-1β levels damage neuronal membranes via lipid peroxidation, serving to reduce memory and learning.[46]

Acute sleep loss similarly induces transcriptional alterations in circadian clock genes, such as *BMAL1, CLOCK, CRY1*, and *PER1*, that further aggravate cognitive impairment.[47] In an animal model, Hou et al determined that sleep deprivation inhibited hippocampal Bmal1 and Egr1 expression levels for more than seven days after sevoflurane inhalation, worsening pathogenically impaired pyramidal neurons, promoting activation of CA1 astrocytes, and significantly reducing cognitive levels (learning and memory especially).[48] In addition, there is clinical trial evidence linking lower intracellular magnesium concentrations to sleep-related cognitive and memory dysfunction.[49] It may well be that magnesium upregulates levels of NR2B-containing N-methyl-D-aspartate (NMDA) receptors critical for synaptic plasticity and memory.[50]

Impact of Altered Sleep Quality on Cardiovascular and Nervous Systems

Postoperative lapses in sleep quality are risk factors for both cardio- and cerebrovascular diseases, including a predisposition to thrombotic events and arrhythmias.[51] One prospective cohort study (N=388) assessing patient status after percutaneous coronary intervention has demonstrated an association between aggregate symptoms of poor sleep and occurrences of major cardiac events, including myocardial infarction, repeat revascularization, and cardiac death.[52] Another study has also confirmed that the biologic *CLOCK* gene is widely expressed in both cardio- and cerebrovascular systems, exerting important regulatory control of heart rate, myocardial growth, cardiac triglycerides, glycogen metabolism, and contractility.[53] The pathogenesis of cardiovascular disease may, therefore, involve sleep deprivation-induced desynchronization of the cardiomyocyte circadian clock.[54,55]

By infringing on sleep–wake rhythms, general anesthesia treads on a major source of sleep disorders, threatening to disrupt the endogenous circadian clock.[24] Ohe et al have demonstrated that sevoflurane increases levels NAD+, thus suppressing mPer2 expression.[56] According to Viswambharan et al,[57] the Per2 circadian clock gene is critical for maintaining normal cardiovascular function. In mutations of Per2, nitrous oxide (NO) and prostacyclin levels secreted by arterial endothelium are reduced, whereas prostaglandin release, endodermal dysfunction, and the potential for thrombosis are heightened, predisposing to cardio- and cerebrovascular pathology. Disorders of circadian rhythm imposed by general anesthetics may impact patient prognosis through similar means. Ma et al have determined potential biomarkers of sleep disorders, having identified altered expression levels of four proteins (PKM, CLU, KNG1, and PFN1) in sleep-deprived rats.[58] Their findings indicate that high-level expression of KNG1, PFN1, and PKM due to sleep deprivation may increase risks of cardiocerebrovascular and neuronal diseases in a rat model. However, CLU exerts a neuroprotective effect by preventing excessive inflammation, inhibiting activation of complement, and enabling clearance of systemic debris. Reduced expression of CLU in conjunction with sleep deprivation may undermine normal cardiovascular and nervous system functions.

Electroacupuncture Alleviates Postoperative Complications that Affect Sleep Quality After General Anesthesia

General anesthetics diminish postoperative sleep quality, as do the postoperative complications of general anesthesia. The reported benefits of electroacupuncture include substantial analgesic and sedative properties, enhanced immune function, and fewer postoperative complications (ie, pain, nausea, and vomiting) due to diminished postoperative sleep quality.[15,59] These are achieved through comprehensive coordination of multiple targets, levels, links, and pathways.[60,61] The specific effects exerted at various acupoints are listed in Table 1.

Mechanisms of Electroacupuncture in Treating Postoperative Pain

Pain caused by surgical trauma is often a considerable challenge for caregivers. Following surgery, 49~74.3% of patients experience moderate or severe levels of pain.[62] However, there is a reciprocal relationship between pain and and sleep. The pain itself disrupts sleep quality, which in turn intensifies pain sensitivity.[63] Although pharmacologic agents administered as epidural, intraspinal, or intrapleural anesthesia, or as patient controlled analgesia (PCA) provide effective postoperative pain relief in most instances, analgesic drugs (especially opioids) are associated with drowsiness, respiratory depression, and sleep disruption. Reduced SWS, dose-dependent REM suppression, variability in total sleep time, and awakening or arousal episodes during sleep may be problematic.[64,65]

Experimental use of electroacupuncture in humans has served to increase pain thresholds by ~20–30%.[66] In a study by Sim et al, electroacupuncture at PC-6 (Neiguan), ST-36 (Zusanli) bilaterally, and subcutaneously along skin incisions proved superior to sham attempts in relieving postoperative abdominal pain, as measured by morphine intake 6–12 h after surgical procedures.[67] Zeng et al also found acupuncture better than oral morphine sulphate in analgesic effect, defined as total pain remission by Visual Analog Scale (VAS) at two, four, and six hours postoperatively.[68] White et al applied electroacupuncture to ST-36 (Zusanli) and LI-4 (Hegu) acupoints at low (2 Hz) and high (100 Hz) frequencies, determining that a combination of low- and high-frequency stimulation released various opioid peptides to synergistically improve postoperative pain and sleep quality.[69] Low-frequency disperse-dense wave stimulation helps induce relaxation and relieve stress, whereas high-frequency sparse-dense wave stimulation exerts strong opioid- and nonopioid-mediated analgesic effects on the spinal cord. This effectively reduces postoperative analgesic use, accelerating surgical recovery and outcomes.[70]

Animal studies focused on mechanisms of electroacupuncture analgesia have established the following: (1) electroacupuncture at LI18 (Futu) in rats relieves acute incisional neck pain, showing an association with downregulation of immune activity (SP, NK-1, and COX-1) and upregulation 5-HT1AR and 5-HT2AR expression levels in dorsal horns of the spine;[71] (2) electroacupuncture-upregulated endocannabinoid seems to directly inhibit pain in a rat model, because CB2 receptor activation inhibits sensory nerve activities;[72] and (3) electroacupuncture at PC6 (Neiguan) to LI4 (Hegu) may alter phosphorylation of the NMDA receptor NR2B subunit in C1–C3 segments of spinal cord, upregulating expression levels of 5-HT2AR mRNA and protein.[73,74]

Mechanisms of Electroacupuncture in Restoring Postoperative Sleep Quality

Patients often develop significant sleep disturbances immediately after surgery, especially if major procedures are involved. Typical polysomnographic manifestations include severe sleep deprivation, sleep fragmentation, or postoperative insomnia.[75] Ye et al have recorded postoperative sleep disorders in 49.00–74.29% of patients with breast cancer. In this scenario, acupuncture at SI9 (Jianzhen) and GB21 (Jianjing) points may actually improve postoperative sleep quality.[76] Xiao et al examined the effects of electroacupuncture on insomnia at various times, discovering that subjective sleep scores and sleep quality improved more decisively in subjects treated between 8:00 and 9:00 PM.[77] A randomized controlled study conducted by Xia et al revealed that acupuncture at GV20 (Baihui) may effectively improve hemorheology indices, promote recovery of brain tissue cells, relieve depression and anxiety, and enhance the postoperative sleep quality of patients after resection of thyroid cancers.[78] Clinical studies have also reported that diminished postoperative sleep quality is common in patients undergoing total hysterectomy. Acupuncture at GV29 (Yintang), ST36 (Zusanli), SP6 (Sanyinjiao), and auricular points may improve the quality and efficiency of postoperative sleep and prolong its duration.[79,80]

Electroacupuncture not only regulates various mechanisms in the body to augment postoperative sleep quality, it also offers good sedation. Dense waves in particular relieve stress and suppress the CNS. There are several mechanisms by which acupuncture may remedy declining postoperative sleep quality. One is by regulating concentrations of 5-HT, norepinephrine, cortisol, melatonin, and other endogenous substances that indirectly influence sleep quality. Studies based on a rat model of insomnia have shown that electroacupuncture may restore normal levels of neurotransmitters (eg, 5-HT and 5-HIAA), IL-1β, and tumor necrosis factor (TNF) and lower levels of norepinephrine and dopamine in

Table 1 The Effect of Electroacupuncture at Different Acupoints

Benefits	Classification	Mechanisms	Acupuncture Sites	Acupuncture Intervention	References
Alleviate pain and improve sleep quality	Clinical trials	(i) Increase the pain threshold.	Neiguan (PC-6), Zusanli (ST-36), and the points along skin incision	After pain scoring, acupuncture for six hours	Zeng et al[68]
		(i) Low frequency discrete dense wave stimulation induce the relaxation of nerve stress. (ii) High frequency sparse dense wave stimulation has a strong opioid and non opioid mediated analgesic effect on the spinal cord. (iii) The combination of low frequency and high frequency electroacupuncture stimulation will release a variety of opioid peptides, which has a synergistic effect of inhibiting pain.	Zusanli (ST-36), Hegu (LI-4)	EA, Low frequency: 2 Hz High frequency:100 Hz	White et al[69]
	Animal experimental studies	(i) Downregulate the immune activity of SP, NK-1 and COX-1 (ii) Upregulate the expression of 5-HT1AR and 5-HT2AR in spinal dorsal horn.	Futu (LI18), Zusanli (ST36), Yanglingquan (GB34)	EA on both sides of acupoints for 30 min, 2 Hz/ 15 Hz, 1 mA in the first 15 min and 2 mA in the latter 15 min.	Qiao et al[71]
		(i) The change of phosphorylation level of NR2B subunit of NMDA receptor in C1-C3 segment of spinal cord.	Neigen (PC-6), Hegu (LI4), Futu (LI18), Zusanli (ST36), Yanglingquan (GB34)	EA, 2 Hz/100 Hz, 1 mA, 30 min	Gao et al[74]
Improve insomnia	Clinical trials	(i) Improve the sleep quality, prolong the sleep time and improve the sleep efficiency.	Jianzhen (SI9), Jianjing (GB21), Quchi (LI11), Shousanli (LI10), Hegu (LI4)	Each acupoint was massaged for three to five minutes at a frequency of 30 times per minute, once in the morning and one in the evening	Ye et al[76]
			Yintang (GV29), Zusanli (ST36), Sanyinjiao (SP6)	Intradermal needle, three days	Qin et al[79]
		(i) Effectively improve hemorheology indexes, promote the recovery of brain cells, relieve depression and anxiety, and improve the sleep quality of patients.	Baihui (GV20)	Mild moxibustion, once a day, 20 minutes each time, seven days	Xia et al[78]

(*Continued*)

Table 1 (Continued).

Benefits	Classification	Mechanisms	Acupuncture Sites	Acupuncture Intervention	References
	Animal experimental studies	(i) Restore the normal levels of neurotransmitters (such as 5-HT and 5-HIAA), IL-1 β and TNF, and reduce the levels of noradrenaline and dopamine in the brain. (ii) The expression of AMPK protein is decreased, the levels of AC COA and Na + – K + – ATPase and plasma corticosterone are increased.	Shenmen (HT7), Sanyinjiao (SP6)	EA, density wave, 5Hz/25Hz, needle retaining for 15 minutes, once a day for five days	Zhu et al[83]
		(i) Increase the expression of mir146a and negatively regulate the Toll-like receptor four signaling pathway, it can stably affect the electrical activity of brain through EEG biofeedback, thus effectively reduce the neural stress function and play sedation and hypnosis effects.	Zusanli (ST36)	EA, density wave, 5Hz/100Hz, 1.0mA, lasted for 30 minutes, once a day for five days	Yang et al[84]
		(i) Enhance the local blood circulation, improve the cerebral ischemia, reduce the level of plasma noradrenaline and dopamine.	Shenmen (HT7), Sanyinjiao (SP6)	EA, density wave, 4 Hz/60 Hz, 1 mA, needle retaining for 15 minutes, once a day for four days	Cheng et al[82]
Reduce complications affecting sleep quality	Clinical trials	(i) Effectively relieve the adverse flow of Qi, regulate the digestive system, and help relax the gastrointestinal tract.	Neiguan (PC-6)	EA, 2–100Hz, alternating wave, not less than 30 minutes, not more than 60 minutes	Gan et al[93]
		(i) Concurrent stimulation of different points may produce synergistic effect on regulating gastrointestinal function impacted by the surgery and anesthetics to prevent PONV as well as accelerating motility of the gastrointestinal track.	Neiguan (PC-6), Hegu (LI4)	Continuous acupuncture during operation	Alizadeh et al[92]
	Animal experimental studies	(i) Improve colonic transit by restraint stress via corticotropin-releasing factor (CRF) type-1 receptors. (ii) Delayed gastric emptying is alleviated by CRF type-2 receptor, which mediates parasympathetic efferent pathway.	Zusanli (ST-36), Tianshu (ST-25).	EA, 1–100 Hz	Takahashi et al[97]
		(i) Evoke upregulation of hypothalamic oxytocin (OXT) and inhibition of parasympathetic nerve activity, and to improve colonic transit associated with acute and chronic heterotypic stress.	Fixed position of abdomen.	EA, 1–100 Hz	Yoshimoto et al[100]

the brain.[81,82] Improved sleep is achieved by electroacupuncture at HT-7 (Shenmen) and SP-6 (Sanyinjiao) acupoints, perhaps due to reduced AMP-activated protein kinase expression, upregulation of acetyl coenzyme A and Na^+/K^+-ATPase levels in paraventricular nucleus, and increased plasma corticosterone levels.[83] Another possibility is that acupuncture may stabilize the electrical activity of human brains through EEG biofeedback, effectively relieving stress and exerting sedative/hypnotic effects. Electroacupuncture at the ST36 (Zusanli) acupoint may prolong sleep times, increasing miR146a expression in sleep-deprived rats, and negatively regulating the Toll-like receptor four signaling pathway. This eventuates in definitive sedative/hypnotic effects and innate immune response regulation.[84,85] Finally, electroacupuncture at HT7 (Shenmen) and SP6 (Sanyinjiao) is known to enhance local blood circulation, improve cerebral ischemia, and lower plasma norepinephrine and dopamine levels in the rat model of insomnia, further enhancing sleep quality.[82]

Mechanisms of Electroacupuncture in Preventing Postoperative Nausea and Vomiting

Postoperative nausea and vomiting (PONV) are among the most common adverse effects of anesthesia, affecting up to 30% of the general population and 80% of high-risk patients within 24 h after surgery.[86,87] Customary treatments of PONV are chiefly pharmaceutical, including 5-HT3 receptor antagonists, NK-1 receptor antagonists, corticosteroids, butyrophenones, antihistamines, anticholinergics, and phenothiazines.[88] Even at lower doses, antiemetic drugs are not free of side effects, such as QTc interval changes, visual disturbances, dry mouth, and dizziness.[89,90]

According to traditional Chinese medicine, surgery may disturb the balanced states of human bodies, diverting movement of qi and blood. Consequently, gastric qi travels upwards (instead of downwards), producing nausea, vomiting, and constipation. Findings of Lv et al and Alizadeh et al indicate that stimulation at points PC6 (Neiguan) and ST36 (Zusanli) helps reverse the adverse flow of qi, regulating the digestive system and relaxing the gastrointestinal tract. These acupoints have proven effective in preventing nausea and vomiting. Concurrent stimulation at PC6 (Neiguan) and LI4 (Hegu) may permit synergistic regulation of gastrointestinal functions impacted by surgery and anesthetics, preventing PONV and promoting gastrointestinal motility.[91,92]

Gan et al have reported outcomes of a randomized double-blind controlled study comparing electroacupoint stimulation at PC6 (Neiguan) with ondansetron use for PONV prevention. They analyzed 75 patients facing major breast surgery under general anesthesia. Electroacupoint stimulation surpassed ondansetron in this regard and was met with greater patient satisfaction.[93] In the context of gastrointestinal surgery, PONV assumes greater importance.[94] An earlier study of rats has underscored that under normal circumstances, electroacupuncture stimulates distal colonic motility and accelerates colonic transit via the sacral parasympathetic efferent pathway.[95] Enhancement of the parasympathetic pathway (ie, vagus and pelvic nerves) is therefore essential to speed colonic motility.[96] Potential mechanisms of electroacupuncture are then as follows: (1) easing of stress via corticotropin-releasing factor (CRF) type-1 receptors to improve colonic transit and mitigation of delayed gastric emptying via CRF type-2 receptors, thus mediating parasympathetic efferent pathway outflow;[97] (2) sympathetic inhibition, preventing presynaptic catecholamine blockade of acetylcholine release in parasympathetic nerves;[98] (3) release of peripheral opioids to relieve pain, curb opioid intake, and combat PONV;[99] and (4) upregulation of hypothalamic oxytocin (OXT) and parasympathetic nerve inhibition, improving colonic transit hampered by acute and chronic heterotypic stress.[100]

Conclusion

In conclusion, general anesthesia may degrade postoperative sleep quality and prolong patient recovery times. Targeted use of electroacupuncture may help increase neurotransmitter levels within the body and regulate the biologic clock gene through various means, conferring improved sleep and other benefits. Large-scale, multicenter trials are still needed to confirm these findings.

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