

Roles of Exosomes and Exosomal MicroRNAs in Postoperative Sleep Disturbance

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Abstract: Postoperative sleep disturbance (PSD) often occurs in elderly patients after major surgery and exerts harmful effects on postoperative recovery. PSD may increase the incidence of postoperative fatigue, severe anxiety and depression, pain sensitivity, and cognitive dysfunction, which can cause or aggravate neurodegenerative diseases via amyloid aggregation and tau accumulation. Exosomes are important carriers that mediate the transfer of active substances and genetic information among cells. Recent evidence has shown that exosomes are involved in the pathogenesis of end-organ morbidity caused by sleep disorders via increasing amyloid plaque formation, transmitting tau protein, regulating neuroinflammation, and increasing blood–brain barrier permeability. Additionally, exosomes may be useful for delivering therapeutic genetic materials, such as microRNAs (miRNAs) and proteins, to exert neuroprotective effects and reduce cognitive impairment. However, the molecular mechanisms underlying this process remain to be fully elucidated. This review focuses on exosome-related pathways and the modulatory role of exosomal miRNAs on the pathogenesis of sleep disturbance and neurodegeneration. Moreover, we discuss the advantages of reducing neurotoxic proteins via exosomal intervention and miRNA regulation. Future research in exosome administration may offer new insights into PSD-related pathomechanisms and therapeutics.

Keywords: postoperative sleep disturbance, exosomes, exosomal miRNAs

Introduction

Postoperative sleep disturbance (PSD) is a common complication after a major surgery,^{1,2} with patients often presenting with reduced sleep quality and duration, early awakening, frequent nightmares, sleep terrors, and sleep-related breathing disorders.³ Polysomnography studies on patients with sleep disorders have suggested occurrence of sleep fragmentation and deprivation as well as decrease in rapid eye movement (REM) and slow-wave sleep (SWS) after surgery.⁴ Additionally, PSD seriously affects the quality of life and increases the difficulty and burden of nursing care. The onset of sleep disorders is related to multiple factors, including age, preoperative complications, type of anaesthesia, degree of surgical trauma, and postoperative pain. Moreover, studies show that sleep disorders can be related to changes in postoperative brain function and increase the risk of postoperative cognitive decline.^{5,6} Early recognition and intervention of sleep disorders can reduce the incidence of mental dysfunction and cardiovascular events, improve prognosis, and shorten the duration of hospital stay.⁷

Exosomes are extracellular vesicles (diameter: 30–100 nm) that contain various active substances, such as proteins, small-interfering (si)RNAs, and microRNAs

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(miRNAs), and act as important carriers that mediate information exchange and material transfer among cells.⁸ Regulatory molecules, such as miRNAs, are transported to recipient cells via exosomes, where they affect biological pathways, leading to changes in cell function and pathology.⁹ Several recent studies have shown that nerve cell-derived exosomes are related to pathological protein aggregation, synaptic morphology, and neuroinflammation, and that changes in exosome biological characteristics and level of dysfunction might be involved in neurodegeneration. Goetzl et al^{10,11} reported that in Alzheimer's disease (AD), P-S396-tau, P-T181-tau, and A β 1-42 are elevated in plasma nerve cell-derived exosomes and can be used to predict the transition from preclinical AD to AD. This review summarised current perspectives regarding the role of exosomes and exosomal miRNAs in PSD pathogenesis. The pathways and pathomechanisms of relevant miRNAs is shown in Table 1.

Postoperative Sleep Disturbance Sleep Structure and Function

The normal sleep–wake cycle is naturally rhythmic.¹² According to the American Academy of Sleep Medicine, sleep–wake states can be divided into wakefulness, non-REM sleep, and REM sleep.¹³ Compared with NREM, REM sleep is associated with stronger physiological activities, fluctuations in blood pressure and heart rate, irregular breathing, and increased brain metabolism.^{14,15}

Long-term reductions in sleep time or complete sleep deprivation can cause cognitive deficits. Limiting sleep time to 4 h to 6 h per night can lead to neurobehavioral impairment upon waking, along with polysomnography results indicating prolonged REM latency and slight increase in SWS.¹⁶ Additionally, sleep deprivation in the time window before and after learning can impair memory and learning ability, as REM sleep deprivation 3–6 h after learning significantly increases levels of brain-derived neurotrophic factor (BDNF) in the CA1 region of the hippocampus.¹⁷ Based on the effectiveness of anti-tumour necrosis factor (TNF)- α therapy, Sochal et al¹⁸ evaluated serum BDNF levels in Crohn's disease patients and healthy controls to assess the relationship between BDNF concentration and the severity of insomnia, and identified a positive correlation between serum BDNF level and results of the Athens Insomnia Scale. These findings suggest that BDNF is involved in PSD-related mechanisms via modulating chronic inflammation.

The interstitial fluid (ISF) of the brain transports soluble proteins, metabolic waste, and excess extracellular fluid along the paravenous drainage pathway, which relies on aquaporin 4 expressed in glial cells. Approximately 55% of soluble A β in the interstitium is cleared by the lymphoid pathway.¹⁹ During sleep, the interstitial volume of the cerebral cortex increases by up to 60%, and the convection of ISF and cerebrospinal fluid (CSF) increases to enable effective clearance of A β . Both sleep and anaesthesia can improve clearance efficiency, indicating that the sleep state itself may be the main factor promoting the clearance of metabolic waste.²⁰

Effects of PSD on Postoperative Outcomes

Patients often show decreased daytime physical strength, functional limitations, and vulnerable emotions, which negatively affect post-surgery recovery. Severe PSD is manifested by changes in the sleep cycle. REM is significantly reduced on the night after surgery, followed by a rebound of REM sleep in the following 2 to 4 days and an increase in the proportion of REM sleep in total sleep time.²¹ REM sleep rebound causes hemodynamic instability and changes in pulmonary ventilation, thereby increasing the incidence of postoperative fatigue, severe anxiety and depression, pain sensitivity, and cognitive dysfunction and also resulting in longer hospital stays.^{22,23} Kessler et al²⁴ found that sleep disorders and low daytime physical activity reflect delayed recovery after discharge. Therefore, sleep intervention may be important for timely rehabilitation. Moreover, improving the sleep environment is recommended to alleviate sleep disturbances in postoperative patients.²⁵ Pharmacological methods, including administration of zolpidem, melatonin, and/or dexmedetomidine, have recently been employed to improve sleep post-discharge. Specifically, administration of zolpidem one night before and on the first night after surgery improves sleep quality and fatigue.^{3,26}

Sleep disturbances in AD patients are characterised by increased duration of awakenings, loss of SWS and REM sleep, and excessive daytime napping. AD patients spend a significant proportion of their day asleep, although this almost completely comprises stages 1 and 2 sleep, which barely compensates for night-time absences of SWS and REM sleep.^{27,28} Thus, abnormal shifts in the sleep–wake rhythm of AD patients may be implicated in PSD, resulting in more prominent cognitive deficits.²⁹

Table 1 Passways and Pathomechanisms of miRNAs in Postoperative Sleep Disturbance

	Expression	Signaling Pathway(s)	Pathomechanism(s)	Reference
miR-26b	Up	Binds to IL-6 mRNA 3'UTR to hinder IL-6 transcription	Suppress microglia activation	Kang et al ⁸⁶
	Up	Inactivates BCL-2-related mitochondrial apoptosis pathway	Neuronal apoptosis	Gao et al ¹¹¹
miR-188-5p	Up	Increases IL-6mRNA by targeting HNRNP A1	Induce cytokine transcription	Mosakhani et al ⁸⁷
miR-155	Up	Induces TLR signalling pathway by suppressing c-Maf, SOCS1	Activate inflammation signaling pathway	Surbhi et al ⁹²
miR-146a	Down	Down-regulates NF- κ B by repressing IRAK1 and TRAF6	Inflammatory regulation	Nakano et al ⁹³
miR-21	Down	Inhibits TLR4/TNF- α /IL-6R pathway	Suppress neuroinflammatory response	Chen et al ⁹⁴
miR-23a	Down	Enhances TNF- α and IL-6 secretions	Induce inflammatory response	Chen et al ⁹⁴
miR-224-5p	Up	Inhibits MALAT1/NLRP3/IL-1 β	Reduce microglia activation	Du et al ⁹⁵
miR-181c	Down	Reduces TLR4/NF- κ B/p65 activation	Inflammatory regulation	Fang et al ⁹⁶
	Down	Promotes neurons remodeling by targeting TRIM2	Dendritic morphogenesis	Fang et al ⁹⁶
miR-132	Down	Enhances synaptic growth by down-regulating p250GAP protein	Synaptic plasticity	Xu et al ⁹⁹
miR-134	Down	Promotes dendrite growth by inhibiting Pumilio2	Dendritic growth	Fiore et al ¹⁰⁰
miR-206	Up	Induces BDNF level	Neurotrophic factor	Zhao et al ¹⁰³
miR-124	Down	Promotes the hypomethylation of BACE1 protein	A β production	Zhang et al ¹⁰⁷
miR-195	Down	Regulates APP and BACE1 expression at the post-transcriptional level	A β aggregation	Sun et al ¹⁰⁸
miR-207	Down	Modulates neurotrophins signaling	Synaptic plasticity	Gao et al ¹¹¹

Exosomes

Exosome Formation and Production

Exosome formation begins in the endocytic system of the cell, with formation of intraluminal vesicles when the cell compartment is recessed inward and buds outward. Although exosomes were originally considered the “garbage bin” of cells, studies have revealed that these vesicles are not specific products of reticulocytes but are rather released from most mammalian cells.³⁰ Later studies reported that exosomes released from mast cells contain ~1200 functional mRNAs, which could be transferred to other cells.³¹ Exosomes participate in several key biological processes by delivering biologically active substances, such as DNA, RNA (mRNAs, miRNAs, and circular RNAs), and proteins. In the CNS, neuronal cells, microglia, and astrocytes secrete exosomes. As mediators of cell–cell communication, exosomes are related to amyloid degradation, brain clearance, and intercellular diffusion of tau, which can induce neuronal apoptosis and lead to neuron loss.³²

Exosome production varies according to different cell states. Dutkowska et al³³ evaluated the expression of interleukin (IL)-1 β , IL-6, and IL-17 in tumours versus surgical margins, and observed significantly higher expression of IL-6 in tumours relative to adjacent tissue, thereby indicating that inflammatory processes play a role in tumorigenesis. Additionally, they evaluated miR-9 and miR-122 as cytokine regulators in pre- and postoperative peripheral blood exosomes, revealing elevated levels of both miRs after tumour resection.

A previous study investigating the expression of tissue inhibitor of metalloproteinases (TIMPs) in tumour and normal neighbouring tissues revealed decreased TIMP3 levels in non-cancerous tissue, whereas preoperative miR-17 expression in serum exosomes was significantly higher in cancer patients compared to healthy controls.³⁴ These findings suggest that exosome production can be influenced by removal of tumour tissue, which could enable the detection of early biomarkers related to tumorigenesis and metastasis.^{35–37}

Exosomes and Sleep Disorders

Rhythmic activities, such as the sleep–wake cycle, are regulated by the circadian rhythm, which is an autonomous, endogenous oscillator in all living organisms and comprises transcriptionally active clock genes (*CLOCK*, *BMAL1*, *PER1*, *PER2*, *PER3*, *CRY1*, and *CRY2*) and their

protein products. Khalyfa et al³⁸ found that *Bmal1*, *Cry2*, and *Per1* expression was significantly reduced in plasma exosomes obtained from mice with sleep-rhythm disorders, indicating that exosomes can act as a bridge between peripheral clock-controlled genes and central rhythms and transmit the effects of circadian-rhythm disorders to target organs, thereby disturbing end-organ homeostasis. In type 2 diabetes, visceral white adipose tissue secretes exosomes that transport functional proteins and RNAs, resulting in alteration of metabolic functions in nearby and distant tissues.³⁹ The associated molecular mechanism may involve α -subunit of hypoxia-inducible factor 1 (HIF-1 α), which regulates oxygen metabolism. Hepatocyte-specific *Hif1a* knockout hindered this metabolic disorder by reducing GLP-1 degradation.⁴⁰ Moreover, several studies investigating the impact of blood oxygen saturation on HIF-1 α mRNA levels showed decreases in these levels following continuous positive airway pressure (CPAP) treatment.^{41–43} These findings support the hypothesis that hypoxia is an independent risk factor for insulin resistance.

The Role of Exosomes in the Pathogenesis of Sleep Disturbance Amyloid Aggregation

Rajendran et al⁴⁴ found that a fraction of A β in MVBs is loaded into exosomes and secreted into the extracellular environment. A β and its products are transferred to MVBs, followed by APP hydrolysis by β -secretase, which mainly occurs in early endosomes. The association between exosomes and A β suggests that inhibition of exosome secretion may reduce AD-like pathological processes; however, exosome function in the process of AD remains controversial.⁴⁵ Exosomes secreted in vivo in brains of APP-overexpressing mice contain higher levels of APP C-terminal fragments (CTFs) compared with normal brain tissue. These data support the hypothesis that an exosome-secretory pathway is beneficial to APP CTFs clearance.⁴⁶ An in vitro study by Kyongman et al⁴⁷ found that exosomes derived from N2a cells counteracted A β -mediated damage to synaptic plasticity and rescued long-term potentiation. Exosomes enhance the uptake of A β into microglia through their surface glycosphingolipids, and ultimately reduce the formation of amyloid plaques.

The effect of sleep in amyloid pathogenesis has been assessed by wakefulness and sleep deprivation studies. Kang et al⁴⁸ monitored hippocampal A β levels in vivo

using microdialysis in both wild-type mice and human APP transgenic (Tg2576) mice. They found that A β levels were significantly elevated during the waking period relative to the sleep period in control and Tg2576 mice, and that ISF A β levels positively correlated with wake-time duration. Xie et al²⁰ reported that sleep facilitates the clearance of A β from the ISF via the glymphatic system as observed on the two-photon imaging of the brain of adult mice, which revealed improved exchange between the glymphatic system and the systemic circulation in the brains of sleeping or anesthetised mice relative to awake mice. These findings suggest that attenuated clearance of A β under sleep-deprivation conditions may also contribute to increased ISF A β levels.

Hypoxia can enhance A β production via increased expression of *BACE1*, which increases the activity of β -secretase and increases APP hydrolysis.⁴⁹ Bu et al⁵⁰ compared blood A β levels under oxygen saturation in 49 patients with OSA, and found that plasma A β levels positively correlated with hypoxic intensity. Additionally, to determine mechanism underlying hypoxia-induced increases in A β , Xie et al⁵¹ investigated the effect of hypoxia on A β metabolism in a human neuroblastoma model stably expressing *APP*. They found that A β export via exosomes increased after exposure to hypoxia, and that expression of CD147, a transmembrane glycoprotein present on exosomes, was also elevated under hypoxic conditions. CD147 is a subunit of γ -secretase, and its degradation is inhibited by the tubulin HOOK1.⁵² Cui et al⁵³ collected bone marrow-derived mesenchymal stem cells (MSCs) from *App* transgenic mice, found A β concentration decreased in the frontal cortex and hippocampus, and memory was improved which possibly due to an exosome-mediated increase in the expression of synapsin 1 and PSD95. Further clarification of the role of exosomes under hypoxic conditions will be beneficial for the prevention and treatment of abnormally increased A β levels caused by sleep disorders.

Tau Release and Transmission

Sleep disorders cause hyperphosphorylation and aggregation of tau protein, resulting in formation of neurofibrillary tangles, neuritic plaques, and other structures. Compared with A β , pathological tau accumulation is more closely related to cognitive decline.⁵⁴ Tau spreads in the brain in a layered manner by first aggregating in the entorhinal cortex and then spreading to the hippocampus before eventually extending to the neocortex and surrounding

areas. Sleep regulates the metabolic homeostasis in neurons. Holth et al⁵⁵ evaluated the effect of the sleep-wake cycle on tau levels in brain-tissue fluids in mice, and found that tau levels increased during the waking state and decreased during sleep; however not all protein levels increased in the CSF after sleep deprivation, and ISF tau level increased following prolonged wakefulness.

The mechanism associated with tau release and diffusion in the brain has long been a focus of tau-pathology research. Recent studies have suggested that tau protein may spread among neurons via exosomes. Wang et al⁵⁶ found that cultured cerebral cortical neuron cells release tau through exosomes. However, compared with cytoplasmic tau, tau in exosomes was in a relatively low-phosphorylation state and accounted for <2% of the total tau level. When intersynaptic connections are broken, exosomes cannot be taken up by neurons, which suggests that tau diffusion via exosomes depends on synaptic-structure integrity. Proteins (annexin 7 and Alix) extracted from the lysates of exosomes that secrete tau are involved in signal transduction and vesicle transport.⁵⁷ The recruitment of these proteins to exosomes may promote tau release; however, the specific molecular mechanism associated with tau release via exosomes remains unknown, and further research is needed to confirm this hypothesis.

In vitro experiments indicate that tau mutations enhance their phosphorylation to promote tau release.⁵⁸ Recent evidence shows that sleep deprivation can activate different kinases and phosphatases in the brain, leading to tau hyperphosphorylation.⁵⁹ However, due to the dephosphorylation of tau by non-specific alkaline phosphatase in the brain, both phosphorylated and dephosphorylated tau proteins can exist outside the cells; therefore, it remains unclear whether phosphorylation promotes tau release.

Blood–Brain Barrier (BBB) Integrity

The BBB is a multicellular vascular structure comprising pericytes, astrocytes, end feet, brain endothelial cells, and the tight junctions between endothelial cells, which control the metabolic exchange between brain and peripheral circulation to protect brain tissue from microorganisms or toxins.⁶⁰ Normal BBB function maintains brain homeostasis. Certain molecules in the brain, such as amyloid protein, TNF- α , and prostaglandins, move in and out of the CNS rhythmically.⁶¹ A β periodically oscillates in the ISF of mouse brain tissues, and circadian-rhythm disorders can affect A β metabolism. Lack of the circadian-clock gene *BMAL1* leads to a decrease in daily A β oscillations

and an increase in amyloid plaque formation.⁶² The transport of A β through the BBB is one of the main steps in the A β metabolism. In rodents, ISF enters the brain parenchyma from the paravascular space of the arteries and flows out from the venous vascular space via the glymphatic system. Sleep can promote this pathway for clearing metabolic waste from the brain, and the interstitial space can increase by up to 60% during sleep, which may promote ISF and CSF convection.²⁰

Decreased clearance of A β through the BBB is one of the mechanisms of pathological A β deposition.⁶³ Transporters at the BBB, such as receptor for advanced glycation end-products, low-density lipoprotein receptor-related protein 1, apolipoprotein, and P-glycoprotein (P-gp), mediate A β transfer from the brain to peripheral circulation.^{64,65} Due to their structural and physiological characteristics, exosomes can enter the brain through the BBB. Pan et al⁶⁶ used recombinant brain microvascular endothelial cell exosomes to increase the expression of P-gp receptors, and found that exosomes enter cells via endocytosis and prevent the lysosome-mediated degradation of P-gp receptors. In mice, increased intracellular P-gp receptor levels reduce A β in the hippocampus and improve cognitive impairment caused by A β aggregation.

After 6 days of sleep restriction, levels of the tight-junction proteins occludin, claudin-1, claudin-5, and zonula occludens (ZO)-2 were significantly reduced in the brain microvessels of mice but returned to the baseline levels in 24 h after resuming sleep.⁶⁷ Khalyfa et al⁶⁸ investigated the effects of plasma exosomes on different types of endothelial cells in 30 children with OSA. Compared with exosomes from children with normal cognitive function, plasma exosomes obtained from children with OSA altered the morphology of ZO-1 and increased BBB permeability, which indirectly affected the microenvironment and neural network in the brain. Following treatment with exosomes transfected with a specific mimic of miR-630, ZO-1 levels increased in endothelial cells, whereas transfection with selective inhibitors of miRNA-630 disrupted tight-junction permeability in endothelial cells.⁶⁹

Exosomal miRNAs miRNAs in Neurodegeneration

miRNAs are noncoding RNAs of ~22 nucleotides that exist widely in eukaryotes. It is estimated that the human genome encodes >1000 functional miRNAs that regulate

the expression of 30% of protein-coding genes.⁷⁰ In the nucleus, primary transcription products are hydrolysed by ribonuclease III Drosha to generate miRNA precursors. These precursors are transferred to the cytoplasm and processed by Dicer to form mature miRNAs that bind to the 3' untranslated region (UTR) of target mRNAs via RISC and Argonaute family proteins. This blocks translation initiation and results in translation inhibition or target degradation.⁷¹ As key regulators of neuronal morphology and function, miRNAs are overexpressed in the brain during different developmental stages of the CNS. Loss of Dicer can cause dopaminergic neuronal death and neurodegeneration, while loss of Dicer in the cortex and hippocampus affects nerve cell development, suggesting that miRNAs play important regulatory roles in various cellular processes, including neuronal morphogenesis, neuronal apoptosis, and neurodegeneration.^{72,73} With the discovery of exosome as a carrier of miRNAs, Xin et al demonstrated that in vitro MSCs stimulate the neurite outgrowth by transferring miR-133b to astrocytes and neurons via exosomes.⁷⁴ The regulatory role of miRNAs has also been noted in the inflammatory response. In animal models of persistent pulmonary hypertension, exosomes mediate a decrease in levels of monocyte chemoattractant proteins and mitogens through miRNAs, thereby inhibiting macrophage infiltration and proinflammatory-mediator release.⁷⁵

Mutations in the apolipoprotein gene are risk factors for AD. The $\epsilon 4$ allele of this gene is a genetic risk factor for protein-related pathology characterised by misfolded protein deposition in neurodegenerative diseases.⁷⁶ Several studies have investigated the role of epigenetic mechanisms (mainly posttranscriptional modifications) in the pathogenesis of neurodegenerative diseases. Specifically, studies compared differential miRNA expression in the AD brain and revealed that miRNA-expression levels in the hippocampus, prefrontal cortex, CSF, and other tissues vary during the course of AD.⁷⁷ Neurodegeneration may result from changes in multiple cellular pathways. For example, miRNAs modulating central components of the amyloid cascade, such as APP and BACE1, have been identified.^{78,79} Moreover, in the CNS, neurons, microglia, and astrocytes can be regulated by miRNAs via exosomes. Immunomodulatory miRNAs are involved in activating the inflammatory response of microglia, which is reportedly a key pathomechanism in AD.⁸⁰ Neurocognitive deficits are linked to loss of synaptic transmission and plasticity in murine models of AD, as well

as AD patients. In this review, we have focused on how various miRNAs exert their modulatory function on AD-related biological pathways.

Putative Roles of miRNAs in Sleep Disturbance and Pathogenesis

The Neuroinflammatory Response

After tissue injury or destruction, the inflammatory response can remove harmful substances and damaged tissues; however, excessive nervous system inflammation can cause neurotoxicity and cell death.⁸¹ Activation of microglia is an important step in initiating the neuroinflammatory response. Cytokines IL-1, IL-6, and TNF- α can induce microglial differentiation into the M1 (proinflammatory) phenotype, whereas IL-4, IL-10, and other cytokines promote their differentiation into the M2 (anti-inflammatory) phenotype.⁸² Additionally, A β deposition, tau phosphorylation, and neurofibrillary tangles can induce microglial differentiation into the M1 phenotype, leading to impaired axonal transport and APP aggregation.⁸³ Damaged neurons can also release A β to cause inflammation, initiating a cycle of continued A β release. CNS inflammation can affect neurotrophic factor levels, thereby damaging synaptic plasticity and leading to decreased nerve regeneration ability.⁸⁴ Wadhwa et al⁸⁵ showed that after 48 h sleep deprivation, levels of IL-1, IL-6, and TNF- α increased significantly in the hippocampus of mice and resulted in impaired spatial memory; however, following minocycline treatment, the BDNF level increased significantly in the brain.

A previous report indicated that miR-26b suppressed microglial activation and decreased the levels of IL-6 in the CA1 region of the hippocampus. This study also showed that miR-26b can bind the 3' UTR of IL-6 to inhibit its transcription, thereby effectively reducing neuronal apoptosis.⁸⁶ Excessive daytime sleep leads to increased levels of miR-188-5p, which targets heterogeneous nuclear ribonucleoprotein A1 (HNRNPA1), a transcriptional regulator of IL-6. A previous study showed that HNRNPA1 overexpression increases IL-6 mRNA expression.⁸⁷ miR-188-5p acts as a tumour suppressor and is related to ventricular remodelling and synaptic plasticity.^{88,89} Ni et al⁹⁰ reported that *BMAL1* expression in microglia is significantly reduced in *App* transgenic mice with a disturbed sleep cycle, whereas mRNA expression of *Tnfa*, *Il1b*, and *Il6* was increased. Experimental results indicate that decreased *BMAL1*

expression reduces the negative regulatory effect of I κ B α on NF- κ B, thus, upregulating NF- κ B and leading to increased *Tnfa*, *Il1b*, and *Il6* transcription.

Toll-like receptors (TLRs) are surface receptors expressed on various cells, including microglia. TLR activation induces. Although TLRs are not exclusively expressed in microglia, the activation of downstream inflammatory signalling pathways by TLRs is an important step in AD pathogenesis.⁹¹ miRNAs can participate in TLR-mediated inflammation signalling pathways at different levels. miR-155 can promote TLR activation by inhibiting negative regulators of TLR, such as c-Maf and suppressor of cytokine signalling 1. In animal models, miR-155 knockout reduces the sleep-promoting effect of endotoxin, increases wakefulness time, and reduces NREM, suggesting its role as a mediator of the regulatory effect of sleep on the immune response.⁹² By contrast, miR-146a acts as an anti-inflammatory regulator in the brain. Upon injection of bone marrow-derived MSC exosomes into the brains of AD mice, microglia differentiated into the M2 phenotype, and astrocytes began to take up exosomes, followed by miR-146-mediated reductions in levels of NF- κ B.⁹³ In addition to miR-155 and miR-146a, miR-21, miR-23, miR-224-5p, and miR-181c regulate proteins involved in the TLR signalling pathway.^{94–96} *TRIM2*, a target of miR-181c, reduces the ubiquitination of nerve-fibre filaments (neurofilament light), and promotes neuronal remodelling in the hippocampus exposed to hypoxia.⁹⁶ Although activation of the inflammatory pathway is clearly an important factor in the development of cognitive impairment, additional research is needed to identify a direct link.

Neuroregeneration

The upregulated transcription of miRNAs in specific brain regions is driven by neuronal activity. For instance, miR-132 expression is transcriptionally stimulated by neural activity and regulated by the cAMP response element-binding protein (CREB) signalling pathway. A β downregulates BDNF levels in AD by inhibiting the transcription of CREB, a downstream target of BDNF, thereby resulting in early decreases in miR-132.⁹⁷ Furthermore, deletion of miR-132 in *App* transgenic mice enhances amyloid plaque accumulation and tau protein phosphorylation.⁹⁸ However, in AD-induced synaptic dysfunction, the effects of miRNA-mediated downstream gene dysregulation remains unknown.

Recent studies have revealed that a lack of miR-132 may lead to a decreased number of dendrites, which is closely related to the loss of synaptic function and cognitive impairment. Following transfection of miR-132 into AD mice, expression of the synaptic proteins PSD95, synapsin-1, and p-synapsin increased significantly in the temporal cortex and memory deficit was partially restored.⁹⁹ Changes in synaptic plasticity and imbalances in the regulatory mechanism are related to the destruction of neural circuits, especially of the complex neuronal network formed by dendritic spines. There exists a complex miRNA-transcription-feedback system in the brain. For example, miR-134 expression is strictly regulated by synaptic activity via the transcription factor MEF2; miR-134 promotes dendritic growth by inhibiting Pumilio2.¹⁰⁰ Additionally, (sirtuin 1) SIRT1 is an NAD⁺-dependent protein acylase that can reduce miR-134 expression via an inhibitor complex containing the transcription factor YY1. A decrease in SIRT1 activity leads to increase in miR-134 levels, resulting in downregulation of CREB and BDNF levels, and impairment of synaptic plasticity.¹⁰¹ Patients with AD exhibit increased miR-134 expression in CSF, and AD exosomes contain higher levels of miR-134.¹⁰² Furthermore, miR-134 can modulate exosomal transport, which is involved in AD pathogenicity, and miR-206-knockdown exosomes increase BDNF expression and inhibit neuronal apoptosis following acute brain injury.¹⁰³ These findings suggest the feasibility of exosomal miRNAs as therapeutic markers.

Cerebral Hemodynamic Changes

Chronic cerebral hypoperfusion and decreased glucose metabolism before cognitive decline are high-risk factors for AD.¹⁰⁴ Due to decreased lung ventilation, brain metabolism and cerebral blood flow are reduced during NREM sleep.¹⁵ Brayet et al monitored cerebral blood flow during REM sleep and found that hypoperfusion of the anterior cingulate gyrus under REM is related to functional defects, which may lead to the onset of AD.¹⁰⁵ miRNAs regulate BACE1 and APP expression at the posttranscriptional level; numerous transcription factor-binding sites have been identified in the promoter regions of *BACE1* and *APP* to complement these miRNAs, suggesting an important role of miRNAs in the pathogenesis of cerebral blood-flow deficiency.¹⁰⁶

In vivo experiments have shown that hypoxia or A β downregulates miR-124 expression in the hippocampus. The underlying mechanism might involve activation of

the exchange protein activated by cAMP (EPAC)–Rap1 pathway. Downregulation of miR-124 promotes hypomethylation of BACE1, increases BACE1 levels in the hippocampus, and leads to increased A β production.¹⁰⁷ Unlike miR-124, miR-195 can reduce A β production under chronic cerebral hypoperfusion and thereby protect neurons; this effect is possibly related to negative regulation of NF- κ B.^{105,108} As an imbalanced miRNA expression is related to neuronal damage caused by cerebral insufficiency, promoting normal miRNA function may thus, have a protective effect on cerebral blood flow.

Apoptosis

Hypoxia, insufficient energy, inflammatory responses, and A β and tau proteins increase the accumulation of ROS in nerve cells and cause mitochondrial DNA mutations. miRNAs and their downstream molecules can regulate apoptosis pathways, as downregulation of miR-26 inactivates the BCL-2-related mitochondrial apoptosis pathway and activates Bax to induce apoptosis of liver cancer cells.¹⁰⁹ Circadian-rhythm disorders affect DNA repair, cell cycle, and cell apoptosis and are associated with neurodegenerative diseases and cancer.¹¹⁰ Gao et al¹¹¹ found that intermittent hypoxia affects the expression of pro-apoptotic and anti-apoptotic proteins in the hippocampus of a mouse model of OSA. Additionally, they found that miR-26b expression in the hippocampus increased three-fold, whereas miR-207 expression remained low in response to intermittent hypoxia. Moreover, miR-207 may play a protective role by participating in autophagy, as a murine model of PD showed that miR-207 inhibited apoptosis of mesencephalon-derived dopaminergic neuronal cells, suggesting that miR-207 may be a potential therapeutic target of PD.¹¹² Recently, some studies investigated the feasibility of modulated miR-125b/p38 mitogen-activated protein kinase (MAPK) signaling to induce varying levels of neurons apoptosis. One study showed that upregulating p38 MAPK via loss of miR125b expression could regulate the expression of apoptosis-specific proteins in SH-SY5Y cells.¹¹³ Furthermore, p38 MAPK was reported to play a role in cascade reactions involved in inflammation, oxidative stress, and A β -mediated cell apoptosis.¹¹⁴

Exosomes and Exosomal miRNAs as Potential Treatment options for PSD

A large body of evidence indicates that sleep disorders may be involved in the pathogenesis of neurodegenerative diseases and increase the risk of dementia.¹¹⁵ Exosomal miRNAs

participate in sleep-disorder pathogenicity via two mechanisms: 1) direct regulation of signal pathway components or 2) regulation of proteins involved in signal pathways or key enzymes.^{116,117} Exosomes can carry altered genetic material derived from diseased cell and appear in early or advanced disease stages. In *App* transgenic mice, rabies virus-modified MSC-derived exosomes significantly reduced soluble A β 40 and A β 42 levels in the brain. Furthermore, following exosome treatment, expression of TNF- α and IL-1 β and levels of glial fibrillary acidic protein decreased, whereas glial cell function was significantly improved.¹¹⁸ In mice, MSC-derived exosomes significantly increased miR-21 levels after hypoxic preconditioning, resulting in downregulation of signal transducer and activator of transcription 3 phosphorylation and inhibition of NF- κ B activation, which reduced the neuroinflammatory response in the brain.⁹⁴ Additionally, other studies reported that miR-21 levels are related to attenuated inflammatory responses, and that reduced miR-206 expression via exosome delivery upregulates BDNF/tropomyosin receptor kinase B/CREB signalling, which exerts a neuroprotective effect on subarachnoid haemorrhage.¹⁰³ Exosomes are naturally produced by human cells. Compared with other carriers of gene therapy, exosomes are advantageous in terms of achieving therapeutic effect, lower immune rejection, and better targeting.¹¹⁹ The delivery of therapeutic RNAs to target cells via exosomes for correcting protein dysfunction is a potential therapeutic strategy for brain diseases characterised by genetic abnormalities.¹²⁰ Notably, exosomal miRNAs can act on different target genes, and expression of one gene can be regulated by multiple miRNAs. This suggests that intervention based on targeting the activity and/or treatment of a single gene would have limited efficacy. Moreover, sequential gene damage caused by sleep disorders requires a multi-pronged therapeutic approach for improving memory and learning dysfunctions.

Conclusion

Exosomes represent potential tools to therapeutically target sleep-disorder pathogenesis. Studies show that exosomes can promote protein misfolding and hinder their successful translation. Furthermore, miRNAs transferred by exosomes modulate the neuroinflammatory cascade, A β generation, and neuronal apoptosis. The role of exosomes in pathological mechanisms related to neuronal damage offers insights into their potential roles as biomarkers of and therapeutic targets for sleep-induced neuronal dysfunction. Elucidating the underlying mechanisms will promote the establishment of sleep-disorder models,

prediction of dementia risk, and devise gene-therapy strategies. Future work should focus on detailed investigation of changes in exosome status and exosomal miRNAs under different types of sleep disturbance for disease prevention and early-stage diagnosis.

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