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REVIEW ARTICLE

The Effect of Melatonin Modulation of Non-coding RNAs on Central Nervous System Disorders: An Updated Review

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Abstract: Melatonin is a hormone produced in and secreted by the pineal gland. Besides its role in regulating circadian rhythms, melatonin has a wide range of protective functions in the central nervous system (CNS) disorders. The mechanisms underlying this protective function are associated with the regulatory effects of melatonin on related genes and proteins. In addition to messenger ribonucleic acid (RNA) that can be translated into protein, an increasing number of non-coding RNAs in the human body are proven to participate in many diseases. This review discusses the current progress of research on the effects of melatonin modulation of non-coding RNAs (ncRNAs), including microRNA, long ncRNA, and circular RNA. The role of melatonin in regulating common pathological mechanisms through these ncRNAs is also summarized. Furthermore, the ncRNAs, currently shown to be involved in melatonin signaling in CNS diseases, are discussed. The information compiled in this review will open new avenues for future research into melatonin mechanisms and provide a further understanding of ncRNAs in the CNS.

Keywords: Central nervous system (CNS), circRNA, lncRNA, melatonin, microRNA, non-coding RNA (ncRNA).

1. INTRODUCTION

Melatonin (*N*-acetyl-5-methoxytryptamine) is a hormone predominantly synthesized in and secreted by the pineal gland [1]. After being released into the blood and cerebrospinal fluid (CSF), melatonin can reach several central nervous system (CNS) regions and all peripheral organs [2]. Melatonin plays a therapeutic role in multiple pathological conditions through various mechanisms, including scavenging free radicals, regulating inflammation, apoptosis or autophagy, and other important processes [3, 4]. Specifically, melatonin also exerts effective neuroprotective effects on CNS diseases such as stroke [5], Alzheimer's disease (AD) [6], traumatic brain injury (TBI), Parkinson's disease (PD), and amyotrophic lateral sclerosis (ALS) [7]. As a versatile molecule, exploring the potential mechanisms by which melatonin works in diseases can facilitate its clinical application.

As a multi-targeted hormone, melatonin has also been extensively studied for its role in regulating non-coding ribonucleic acid (ncRNA); ncRNA is defined as RNA that is not translated into a protein. Recent sequencing results revealed that at least 70% of the genome in humans is transcribed into RNA; however, no more than 2% of the genome encodes proteins [8, 9]. According to a relatively broad threshold, 2 subclasses of ncRNA can be distinguished: small or short ncRNAs and long ncRNAs (lncRNAs) [10]. RNAs can also be divided into different types according to their structure and function, such as transfer and ribosomal RNAs, the most well-known ncRNAs. MicroRNA (miRNA), circular RNA (circRNA), and piwi-interacting RNAs are also members of this family. With deepening research in the field of genomics, the roles of these ncRNAs have been further interpreted. The main functions of ncRNAs include, but are not limited to, participation in and regulation of translation, RNA modification and degradation, serving as nucleic acid carriers, and regulating gene expression [11]. In addition to these physiological functions, ncRNAs are also involved in various pathological conditions such as cancer [12], inflammation [13], cardiovascular disease [14], and a variety of brain disorders [15]. Therefore, ncRNAs will likely serve as biomarkers or therapeutic targets for many diseases in the future.

Many studies have found that melatonin can participate in or interfere with disease development by regulating ncRNA expression. Gu *et al.* found that melatonin can inhibit miRNA-155 (miR-155) expression by downregulating c-myeloblastosis (c-MYB) expression, thereby repressing glioma cell proliferation, migration, and invasion [16]. A study has also revealed that melatonin can inhibit RAF1 expression and the oncogenic pathway downstream of RAF1 through promoting the expression of let7i-3p, thus finally

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suppressing the growth and metastasis of liver cancer cells [17]. Furthermore, lncRNA has also been reported to be regulated by melatonin, consequently suppressing the progression of hepatocellular carcinoma [18]. Thus, ncRNAs are regulated by melatonin in various pathological conditions. Therefore, future studies should focus on the interaction of melatonin with ncRNAs, providing a basis for exploring pathological mechanisms and potential therapeutic targets. This review evaluates the relationship between ncRNAs and various CNS diseases including stroke, TBI, spinal cord injury (SCI), AD, PD, epilepsy, and glioma; furthermore, based on findings involving the role of melatonin in ncRNA in these diseases, a new regulatory mechanism is proposed regarding melatonin in CNS diseases and in the synthesis of melatonin itself. These results will help broaden the research horizon of both melatonin and ncRNA.

In the current review, we mainly used "melatonin", "Central Nervous System Diseases", "Stroke", "Cerebral Hemorrhage", "Subarachnoid Hemorrhage", "Traumatic Brain Injury". "Spinal Cord Injury", "Alzheimer Disease", "Parkinson Disease", "Epilepsy", "Glioma", "Glioblastoma", "MicroRNA", "LncRNA", "CircRNA", "Noncoding RNA" as keywords to search the literature.

2. MicroRNAs

MiRNAs are a class of ~18–25 nucleotide-long ncRNAs that play a central part in cell proliferation, differentiation, and survival by binding to target messenger RNAs (mRNAs), leading to inhibited mRNA translation or degradation [19]. MiRNAs were discovered in 1993 [20]; since then, over 30,000 unique miRNA sequences have been found in over 200 fully-sequenced species. Many studies have extensively explored miRNA structure, function, biogenesis, and mechanisms of action [21]. In the field of CNS diseases, the miRNA might be one of the most important ncRNAs involved in pathological processes. Studies have found that many miRNAs are changed in the brain, blood, CSF [22], and/or saliva after CNS injuries [23], including stroke, whether hemorrhagic [24] or ischemic [21, 24, 25], as well as TBI [26], SCI [27], and various neurodegenerative diseases, including PD [28], AD [29], and ALS [30]. Furthermore, miRNAs are involved in axon degeneration [31], epilepsy [32], and many CNS tumors such as meningioma [33], glioma [34], and pituitary tumors [35]. In fact, as one of the most widely studied ncRNAs, miRNAs have been closely related to the prevention, diagnosis, and treatment of these diseases [36].

3. LONG NON-CODING RNA

In addition to miRNA, lncRNA has a very close relationship with the nervous system. Compared to miRNA, lncRNA is even more remarkable in its CNS specificity. Notably, 40% of 10 000-50 000 lncRNA genes (equivalent to 4000-20 000) in the human genome are expressed specifically in the brain [37], indicating that lncRNAs may play a crucial role in the physiological or pathological condition of the CNS. Their mechanisms of action include both transcriptional and post-transcriptional regulation, leading to gene expression alterations or serving as competing endogenous RNA (ceRNA) and miRNA sources; lncRNA is also involved in RNA degradation [38].

LncRNA is widely involved in the developmental regulation of the CNS, including brain tissue and proliferation and differentiation of stem cells and progenitor cells. Moreover, it has been demonstrated that lncRNA controls stem cell renewal and the formation of particular lineages in the embryonic mouse brain [37]. A recent study also found that compared to protein-coding genes, lncRNA provides more information about cell type identity during mammalian cortical development [39]. Besides, some lncRNAs (KCN2AS and BC1/200) also participate in controlling neuronal plasticity [37, 40]. LncRNA has also been extensively studied in CNS diseases. For example, lncRNAs can be used to diagnose acute stroke and predict outcome after stroke [41]. In addition, the lncRNA-MALAT1 has been shown to regulate neuroinflammation after TBI [42]. LncRNA also plays an indispensable role in the onset and progression of glioma, regulating tumor cell proliferation, angiogenesis, and drug resistance [43].

4. MELATONIN, microRNA, LONG NON-CODING RNA, AND THE PATHOLOGICAL PROCESS OF CENTRAL NERVOUS SYSTEM DISEASES

As mentioned above, melatonin is a multi-targeted hormone and has been extensively studied in CNS diseases. Recent studies regarding melatonin's function in neurological diseases and CNS tumors (represented by glioma) are listed in Tables **1** and **2**, respectively. The pathological processes of different CNS diseases are complex; however, some share common mechanisms such as inflammation, cell death (especially neuronal apoptosis), oxidative stress, and autophagy. Although the pathological mechanisms of CNS diseases may vary, it is important to understand the role of melatonin and ncRNA in these diseases by studying their effect on these common pathways.

5. INFLAMMATION

Although the role of inflammation has not been conclusively determined to be either beneficial or detrimental, it is generally believed that neuroinflammation is crucial to a variety of CNS diseases, including TBI [44], neurodegenerative diseases [45], and stroke [46, 47]. The relationship between ncRNA and inflammation has been reported in the nervous system. For example, inflammatory mechanisms in AD brains can provoke increased miRNA-146a (miR-146a) expression, which, in turn, modulates the inflammation itself [48]. Many miRNAs, such as miR-22, miR-203, and miR-124, have been shown to modulate inflammatory signaling after cerebral ischemia, mainly through targeting cytokine expression in immune cells [21].

Microglia have emerged as central players in CNS pathological processes, especially neuroinflammation [49]. As the resident macrophages of the brain, microglia activation results in inflammation under a variety of stimuli. Therefore, studying the relationship between ncRNA and microglia will contribute to the understanding of the role of ncRNA in neuroinflammation. Ponomarev *et al.* found that miR-124 is highly expressed in microglia. Furthermore, miR-124 plays

Table 1. Melatonin regulation mechanisms in common CNS diseases.

CNS Disease	Mechanism Involved	Year	Authors
Ischemic stroke	regulates neuroinflammation by modulating microglia	2019	Azedi F *et al* [196]
Ischemic stroke	reduces oxidative/inflammatory stress, preserves BBB integrity, and enhances endogenous neurogenesis	2012	Chern CM *et al* [197]
Ischemic stroke	increases the antioxidant response	2013	Ritzenthaler T *et al* [198]
Ischemic stroke	enhances the intrinsic antioxidant status, inhibits the acid-mediated rise in intracellular calcium levels, decreases apoptotic cell death	2014	Bhattacharya P *et al* [199]
Ischemic stroke	decreases extracellular glutamate-derived ROS	2016	Patiño P *et al* [200]
Ischemic stroke	prevents cell death and mitochondrial dysfunction *via* a SIRT1-dependent mechanism	2015	Yang Y *et al* [142]
Ischemic stroke	decreases apoptosis through reduced p53 phosphorylation by the PI3K/Akt pathway	2017	Kilic U *et al* [201]
Ischemic stroke	modulates glutamatergic impairment, synaptic dysfunction, apoptotic markers, and neurodegeneration	2019	Shah FA *et al* [202]
Ischemic stroke	decreases apoptotic neuronal cells	2017	Chumboatong W *et al* [203]
Ischemic stroke	attenuates post-ischemic ER stress	2018	Lin YW *et al* [204]
Ischemic stroke	attenuates IR-induced ER stress dependent autophagy	2017	Feng D *et al* [205]
Ischemic stroke	promotes remyelination	2018	Chen BH *et al* [206]
Hemorrhagic stroke	impacting apoptosis, inflammation, oxidative stress, DNA damage, brain edema, and BBB damage; reduces mitochondrial membrane permeability transition pore opening	2018	Wang Z *et al* [4]
Hemorrhagic stroke	suppresses microglial necroptosis	2019	Lu J *et al* [84]
Hemorrhagic stroke	protects against neuronal apoptosis	2018	Xu W *et al* [207]
Hemorrhagic stroke	reduces the brain water content and neuronal apoptosis	2017	Zhao L *et al* [144]
Hemorrhagic stroke	inhibits NLRP3 inflammasome-associated apoptosis	2016	Dong Y *et al* [208]
Hemorrhagic stroke	inhibits mitophagy-associated NLRP3 inflammasome	2017	Cao S *et al* [209]
Hemorrhagic stroke	represses the inflammatory response and apoptosis	2015	Chen J *et al* [77]
Hemorrhagic stroke	modulates apoptosis signaling pathways	2018	Yang S *et al* [169]
Hemorrhagic stroke	suppresses excessive neuronal apoptosis and autophagy	2018	Shi L *et al* [210]
TBI	negatively regulating inflammation activation and IL-1β secretion *via* the autophagy of damaged mitochondria	2017	Lin C *et al* [211]
TBI	ameliorates cortical neuronal apoptosis	2016	Wu H *et al* [212]
TBI	enhances autophagy	2015	Ding K *et al* [213]
TBI	diminishes astrocyte reactivity and neuronal cells apoptosis	2015	Babaee A *et al* [214]
TBI	prevents inflammation and oxidative stress *via* the Nrf2-antioxidant response element pathway	2019	Wang J *et al* [215]
TBI	protects against brain injury-induced oxidative stress, neuroinflammation, and neurodegeneration *via* AMPK/CREB signaling	2019	Rehman SU *et al* [216]
TBI	provides protection against BBB hyperpermeability *via* matrix metalloproteinase-9 inhibition	2016	Alluri H *et al* [217]
SCI	anti-inflammatory effect	2017	Paterniti I *et al* [218]
SCI	inhibits neuronal apoptosis	2017	Shen Z *et al* [219]
SCI	against oxidative stress damage	2017	Yuan XC *et al* [220]

(Table 1) contd….

CNS Disease	Mechanism Involved	Year	Authors
SCI	acting on inflammatory cytokines	2016	Krityakiarana W *et al* [221]
SCI	promotes neural cell differentiation	2016	Gao Y *et al* [222]
SCI	inhibits pro-inflammatory responses and promotes M2 polarization of microglial/macrophages in the spinal cord in the early stage of SCI	2019	Zhang Y *et al* [223]
SCI	suppresses inflammasome activation	2019	Xu G *et al* [224]
SCI	enhancing autophagy as well as reducing apoptosis after SCI in rats, probably *via* the PI3K/AKT/mTOR signaling pathway	2019	Li Y *et al* [225]
PD	amelioration of oxidative stress due to dose-dependently scavenging of hydroxyl radicals, restoration of glutathione levels, and elevating antioxidant enzyme activity	2018	Paul R *et al* [226]
PD	attenuates MPTP-induced neurotoxicity by preventing CDK5-mediated autophagy and SNCA/SNCA aggregation	2015	Su LY *et al* [227]
PD	alleviates neurotoxicity	2017	Li Y *et al* [228]
PD	against 6-hydroxydopamine-induced oxidative stress	2015	Ozsoy O *et al* [229]
PD	enhances neural stem cell differentiation and engraftment by increasing mitochondrial function	2017	Mendivil-Perez M *et al* [230]
PD	inhibiting oxidative stress and Drp1-mediated mitochondrial fragmentation	2016	Chuang JI *et al* [231]
AD	attenuates memory impairment, A β accumulation, and neurodegeneration by mitigating mitochondrial damage	2015	Rudnitskaya EA *et al* [232]
AD	increases hippocampal synaptic density and the number of excitatory synapses, decreases the number of inhibitory synapses, and upregulates pre- and post-synaptic proteins	2015	Stefanova NA *et al* [233]
AD	effectively alleviates mitochondrial damage and decreases the expression of p-tau and some key apoptosis proteins	2018	Gong YH *et al* [234]
AD	reduces neuronal cell death	2015	Buendia I *et al* [235]
AD	attenuates memory impairment, neuroinflammation, and neurodegeneration possibly through the RAGE/NF-K B/JNK pathway	2015	Ali T *et al* [236]
AD	improves mitochondrial structure and function by enhancing mitochondrial biogenesis and decreasing amyloidogenic APP processing in AD	2019	Wang CF *et al* [237]
AD	activating antioxidant systems	2019	Khatoon R *et al* [238]
AD	restores autophagy flux	2019	Luengo E *et al* [239]
AD	blocks A β -induced neurotoxicity and reduces neuronal apoptosis	2018	Zhao Y *et al* [71]
AD	protects against apoptosis	2015	Shukla M *et al* [240]
AD	anti-apoptotic and antioxidant	2015	Al-Olayan EM *et al* [241]
AD	prevents PrP (106-126)-induced neuronal cell death by regulating anti-apoptotic proteins and mitochondrial pathways	2014	Jeong JK *et al* [242]
AD	ameliorating oxidative brain damage, stress kinase expression, neuroinflammation, and neurodegeneration	2019	Muhammad T *et al* [243]
AD	maintaining BBB integrity	2017	Liu WC *et al* [244]

a crucial role in inhibiting the activation of microglia and macrophages; *in vivo* administration of miR-124 suppresses experimental autoimmune encephalomyelitis (EAE) by affecting macrophages and microglia [50]. Besides miR-124, microglia are also enriched with miRNA-223 (miR-223) [51]; deficiency of miR-223 suppresses pathogenic neuroinflammation and demyelination during EAE in mice by regulating microglia autophagy [52]. Inflammatory microglia can secrete miRNA enriched extracellular vesicles that then transfer miR-146a-5p, a microglia-specific miRNA, to neu-

Table 2. The mechanism of melatonin in glioma.

Glioma Cell Lines used	Mechanism Involved	Year	Authors
U87, U373, and U251	repress glioma cell proliferation, migration, and invasion	2017	Gu J *et al* [16]
U251	anti-migratory and anti-invasive effects *via* the ROS- α v β 3 integrin-FAK/Pyk2 signaling pathways	2015	Xu CS *et al* [245]
293T, A172, and U87MG	activate apoptosis signaling in GBM cells by inhibiting TFEB (transcription factor EB) expression, and oligomerization	2019	Sung GJ *et al* [246]
T98G and U251	inhibition of migration and invasion of glioma cells by melatonin is associated with its inhibition of the oxidative stress pathway	2012	Wang J *et al* [247]
A172 and U87	increase cell sensitivity to TRAIL-induced cell apoptosis	2010	Martín V *et al* [248]
U251 and U87	suppress hypoxia-induced glioblastoma cell migration and invasion *via* HIF-1 α inhibition	2013	Zhang Y *et al* [249]

α v β 3, alpha-v beta-3; FAK/Pyk2, focal adhesion kinase/proline-rich tyrosine kinase 2; GBM, glioblastoma multiforme; TRAIL, tumor necrosis factor-related apoptosis-inducing ligand; HIF-1 α , hypoxia-inducible factor 1-alpha; ROS, reactive oxygen species.

rons. Through neuroligin 1 downregulation, miR-146a-5p causes alterations of the synapse, including restricted synaptic function and excessive synapse destabilization, resulting in a pathological loss of synapses; these alterations underlie synaptic dysfunction occurring in chronic inflammation [53]. Moreover, miRNA-9 (miR-9) plays a key role in microglial activation through suppressing monocyte chemotactic protein-induced protein-1 expression and subsequent downstream activation of nuclear factor-kappa B (NF-κB) [54]. Notably, miR-9 can specifically target transgenic expression in microglia; thus, it can be used to monitor and isolate activated resident microglia [55]. In addition to activation, microRNAs can also affect microglial polarization. MiR-155 is considered as a pro-inflammatory miRNA and is crucial for the polarization of M1 microglia, also known as the inflammatory phenotype [56]. Thus, miR-155 inhibition can be a potential therapy for neuroinflammation [57].

LncRNA-1810034E14Rik was significantly decreased in primary microglia after oxygen-glucose deprivation, an experimental *in vitro* model of ischemic stroke. Overexpression of 1810034E14Rik ameliorated ischemic brain injury *in vivo* by reducing microglia activation, likely by inhibiting the NF-κB pathway [58]. LncRNA-H19 promotes the activation of hippocampal microglia and astrocytes, as well as the inflammatory response in epilepsy, in rats *via* the Janus kinase (JAK)/signal transducer and activator of transcription (STAT) signaling pathways [59]. Thus, manipulating ncRNA to regulate microglia and neuroinflammation could be an effective strategy for the treatment of CNS diseases.

There is some progress in investigating the ability of melatonin to regulate neuroinflammation *via* miRNA or lncRNA. Melatonin was found to repress neonatal brain inflammation by reducing the expression of miRNA-34a (miR-34a), which then directly targeted sirtuin-1 (SIRT1), a negative molecular regulator of an inflammatory response [60]. Importantly, the expression of lncRNA-CCL2 can stimulate the release of proinflammatory cytokines and is downregulated by SIRT1 [61]. Therefore, it is reasonable to speculate that the regulation of melatonin *via* lncRNA-CCL2 may exist, although no such effects have been investigated to date.

6. OXIDATIVE STRESS

Oxidative stress is involved in the pathological processes of most CNS diseases [62]. More importantly, the antioxidant function is one of the earliest studied characteristics of melatonin. ncRNAs have been reported to regulate oxidative stress damage in many CNS diseases. Oxidative stress is considered to cause neurodegeneration in AD, and several miRNAs have been shown to affect AD-related oxidative stress damage. Overexpressed miRNA-186 alleviated oxidative stress-induced neuronal injury by inhibiting the JAK-STAT pathway in a rat model of AD [63]. Furthermore, the overexpression of miRNA-330 could suppress oxidative stress injuries and alleviate mitochondrial dysfunction in AD mice by targeting the *VAV1* gene *via* the mitogen-activated protein kinase (MAPK) signaling pathway [64]. Moreover, lncRNA maternally expressed 3 (MEG3) upregulation inhibited oxidative stress and inflammatory injuries in AD rats *via* the inactivation of the phosphoinositide 3-kinase/protein kinase B (PI3/Akt) pathway [65]. By contrast, the downregulation of lncRNA SOX21-antisense divergent transcript 1 and lncRNA activated by TGF-β relieves neuronal oxidative stress injury [66]; hence, these lncRNAs may be related to the progress of AD. Oxidative stress damage associated with ncRNAs has also been extensively studied in ischemic stroke. Notably, miR-23a-3p inhibited oxidative stress and reduced cerebral ischemia-reperfusion (I/R) injury [67]. MiR-106b-5p was also found to suppress oxidative stress and apoptosis in cerebral I/R injury [68]. In glioma, the deregulation of miR-33a may promote tumor development by regulating SIRT6 expression. Studies in the near future should focus on how these regulatory mechanisms can be used to treat diseases [69].

At present, some studies have begun to explore the role of melatonin in oxidative stress by acting on ncRNA. The senescence of cardiac progenitor cells (CPCs) due to patho-

logical stimuli leads to the decline of CPC functions and regenerative potential. Melatonin remarkably inhibits premature senescence of CPCs in response to oxidative stress by acting on the H19/miR-675/USP10 pathway [70]. Melatonin alleviated amyloid beta (Aβ)-induced oxidative stress in primary neurons by attenuating the downregulation of miRNA-132 (miR-132) and the upregulation of phosphatase and tensin homolog (PTEN) and forkhead box O3 (FOXO3a), two important signaling molecules of miR-132, ultimately reducing neurotoxicity [71]. In a study of radiation-induced lung injury, melatonin was shown to reduce oxidative stress damage by restoring downregulated miRNA-30e levels [72]. In view of these findings, it is necessary to further perform research regarding how melatonin's antioxidant function is related to ncRNA regulation. If melatonin regulates oxidative stress through ncRNAs in CNS disease, this may broaden its clinical application.

7. APOPTOSIS AND OTHER FORMS OF CELL DEATH

Various types of cell death occur in many CNS diseases, including apoptosis, an essential form of cell death. Both miRNA and lncRNA, either alone or upon interaction with each other, extensively modulate the interrelated steps and mediators of programmed cell death, including apoptosis [73]. MiRNAs directly or indirectly affect BAX, a protein of the pro-apoptotic B-cell lymphoma 2 (Bcl2) family, to modulate intrinsic apoptosis [73]. By upregulating proapoptotic Bcl2 family members, miR-23a and miR-27a contribute to neuronal cell death after a TBI [74]. Bcl2-interacting mediators of cell death or related mechanisms can also be targeted to allow miRNA to modulate intrinsic apoptosis. In addition, the anti-apoptosis effect of miR-21 in microglia-mediated neuronal injury was reported to be dependent on Fas ligands [75]. This means that microRNAs can inhibit extrinsic apoptosis by interacting with death ligands. LncRNA can also participate in apoptosis regulation on various levels [76]; more importantly, lncRNA and miRNA can interact with each other to achieve more precise apoptosis regulation.

Several studies have reported that melatonin can inhibit apoptosis after subarachnoid hemorrhage (SAH) [77]. Further research on ncRNAs has led to a deeper understanding of the mechanisms by which melatonin regulates apoptosis. After SAH, melatonin can regulate early brain injury by altering the expression of lncRNA H19 to interact with miR-675 and let-7a, which then influence two important modulators of cell apoptosis: P53 and neural growth factor (NGF). Melatonin inhibits the proliferation of U87 glioma cells by promoting cell apoptosis *via* negatively regulating miR-155 expression [16]. Moreover, miRNA-16 (miR-16) is associated with the role of melatonin regarding tumor cell apoptosis. MiR-16-5p was significantly highly expressed in melatonin-treated gastric cancer cells by upregulating the miR-16-5p-SMAD3 pathway. In addition, melatonin was found to induce apoptosis of these cells, thus, suggesting a promising target for designing therapeutic gastric cancer strategies [78].

Pyroptosis, a novel form of inflammatory programmed cell death, differs from necrosis and apoptosis [79]. A recent study found that melatonin suppresses inflammasome-induced pyroptosis by inhibiting gasdermin D (GSDMD), an executive molecule of pyroptosis, in mouse adipose tissue [80]. Additionally, GSDMD-mediated pyroptosis can be suppressed in microglial cells by melatonin. Zhang *et al.* explored the mechanism by which melatonin inhibits endothelial cell pyroptosis *via* ncRNA. Their study results suggest that melatonin inhibited the nucleotide-binding domain leucine-rich repeats family protein 3 (NLRP3) inflammasome and pyroptosis by regulating the lncRNA MEG3/miR-223/NLRP3 axis. MEG3 overexpression and miR-223 knockdown can abolish the inhibitory effect of melatonin on pyroptosis; therefore, melatonin may function by downregulating the expression of MEG3 and limit its role as a form of ceRNA for miR-223 [81].

In addition to the apoptosis and pyroptosis mentioned above, there are many other forms of programmed cell death that are gradually being discovered, such as necroptosis. Necroptosis is an important mechanism of cell death in brain injuries after intracerebral hemorrhage (ICH); furthermore, necroptosis inhibition may be a potential therapeutic ICH intervention [82]. Melatonin has been shown to inhibit necroptosis in various diseases, including ICH [83-85]. Moreover, many ncRNAs, including miR-223, miR-21, and miR-200a-5p, have been found to regulate necroptosis [86, 87]. Additionally, ferroptosis, an iron- and reactive oxygen species (ROS)-dependent form of programmed cell death, is involved in a variety of CNS diseases [88, 89]. Although not in the CNS, recent research has found that melatonin can inhibit heme-induced platelet activation and ferroptosis [90]. Like necroptosis, ferroptosis is also closely related to ncRNAs such as miR-9 and miR-137 [91]. These studies suggest that the mechanism by which melatonin alleviates these forms of cell death by ncRNA deserves further exploration in future studies.

8. AUTOPHAGY

Autophagy plays an important role in CNS diseases. This cellular stress response mechanism normally plays a key role in CNS physiology; however, uncontrolled and exacerbated autophagy may contribute to disease pathologies such as AD and PD [92]. ncRNA has been shown to be involved in regulating autophagy and disease progression in many CNS diseases. It has recently been reported that autophagy enhancement ameliorated the pathogenesis of multiple sclerosis or EAE by limiting neuroinflammation [52, 93, 94]. The regulation of autophagy by miR-223 plays a role in EAE progression; importantly, inhibiting miR-223 can regulate autophagy and limit uncontrolled or harmful autophagic activity in cells. In addition, miR-223 deficiency suppresses pathogenic neuroinflammation and demyelination in EAE. Blocking autophagy could attenuate these protective effects; hence, there is a close relationship between miR-223, autophagy, and neuroinflammation [52]. In addition, there are other ncRNAs that regulate autophagy in CNS diseases. In an epilepsy mouse model, miRNA-421 suppresses hippocampal neuron autophagy by inhibiting the toll-like receptor (TLR) pathway [95], while the down-regulation of lncRNA metastasis-associated lung adenocarcinoma transcript 1 activates the PI3K/Akt signaling pathway to protect hippocampal neurons against autophagy in rats with epilepsy [96].

MiRNA-181a can regulate autophagy in PD by inhibiting the p38 MAPK/c-Jun N-terminal Kinases (JNK) signaling pathways [97]. Furthermore, miRNA-519a, miRNA-93, and lncRNA LINC00470 influence autophagy in glioblastoma [98, 99].

There are many studies investigating the mechanism of autophagy regulation *via* melatonin in CNS diseases. In fact, melatonin has a dual effect on autophagy [92]. Although this increases the complexity of its specific regulatory mechanisms, it also justifies the importance of an autophagic balance for CNS homeostasis. Some studies have reported that melatonin can affect autophagy through ncRNA. In the experiment by Carloni *et al.*, although there is no direct evidence that melatonin affects autophagy through microRNA, the authors found that after neuroinflammation, melatonin can increase the expression of SIRT1 that regulates the autophagy process [60]. Thus, we hypothesized that melatonin could indirectly affect autophagy after CNS diseases through the miR-34a/SIRT1 signaling pathway. Another example related to SIRT1 was proven in non-alcoholic fatty liver disease, in which melatonin influences hepatocyte autophagy through the miR-34a-5p/Sirt1 pathway [100]. According to the above results, future research on melatonin and ncRNA should focus on the role of SIRT1.

9. NON-CODING RNAs THAT MEDIATE THE ROLE OF MELATONIN IN CENTRAL NERVOUS SYSTEM DISEASES

9.1. Melatonin synthesis and microRNA

Melatonin is not only a multi-target hormone but is also synthesized and released normally by the pineal gland. Melatonin synthesis alterations may be involved in various pathological processes. For example, melatonin levels decline in the elderly, especially in patients with AD [101]. Inhibiting melatonin synthesis induces AD-like pathological changes and spatial memory deficits in rats, which are reversed by supplementation with exogenous melatonin [102]. Notably, miRNAs such as miR-7 [103], miR-483 [104], and miR-325 [105] can affect melatonin synthesis. By acting as a linking molecule between the leptin-mediated and norepinephrine-mediated signaling pathways, miR-7 inhibits melatonin synthesis in pig pineal glands [103]. Interestingly, the miR-7 expression also changes in some CNS diseases. Voltage-dependent anion channel proteins (VDACs), required for functional mitochondria and neuronal survival, are downregulated after ischemic stroke. This effect is attributed to elevated miR-7; thus, targeting miR-7 after ischemia and increasing VDAC expression can subsequently confer neuroprotection [106]. However, whether the detrimental effect of an miR-7 increase is related to reduced melatonin synthesis cannot be confirmed at present.

Clokie *et al.* summarized a group of miRNAs that show striking tissue specificity and strong developmental changes in the pineal gland, laying the foundation for future research on the role of miRNA in this organ [104]. They found that miR-483 can impact aralkylamine N-acetyltransferase (AANAT) levels, and ultimately influence melatonin synthesis. At present, there are few studies about miR-483 in CNS diseases; thus, research can be further expanded in this field. Disrupted melatonin synthesis is also associated with increased miRNA-451 (miR-451) levels in patients with autism spectrum disorder [107]. MiR-451 is also expressed in patients with glioblastoma multiforme (GBM) and indicates a poor prognosis. Specifically, miR-451 reduces glioma cell migration but promotes its proliferation [108]. In addition, miR-451 can regulate the balance of proliferation and migration in glioma cells in response to changes in glucose levels [109]. This association of tumor metabolism-related effects with melatonin needs further validation.

9.2. Melatonin and microRNA-124

MiR-124, a brain-enriched miRNA, can promote nervous system development [110]. Melatonin can regulate miR-124 levels by directly promoting protein exchange activated by cyclic AMP expression, thus, reducing memory deficits and synaptic disorders in an AD model. This suggests a new epigenetic mechanism through which melatonin reduces synaptic disorders [101]. MiR-124 is also abundant in the pineal gland and targets an enzyme for Asmt-catalyzed *O*-methylation of *N*-acetyl serotonin, known as Mat2a, to form melatonin [104]. This suggests that it may also be involved in melatonin synthesis regulation, although no other experimental results have confirmed this conclusion. MiR-124 is important for the CNS and has been studied with respect to various diseases; Sun *et al.* reviewed the relationship between miR-124 and CNS disease [111]. MiR-124 induces neuroprotection and functional improvements, partly *via* the apoptosis-inhibiting pathway [112], after focal cerebral ischemia. This suggests miR-124 may serve as a novel therapeutic strategy for neuroprotection and functional recovery upon stroke onset [113].

The miR-124/tyrosine-protein phosphatase non-receptor type 1 pathway is a critical mediator of synaptic dysfunction and memory loss in AD [114]. Furthermore, miR-124 loaded nanoparticles can enhance brain repair in PD; the possible mechanisms involve regulating apoptosis and impairing autophagy processes by miR-124 [115, 116]. MiR-124 is also involved in TBI and SCI pathogeneses. It was demonstrated that miR-124 promoted the M2 polarization of microglia, further improving hippocampal neurogenesis and functional recovery after TBI; the M2 polarization effect was mediated by inhibiting the TLR4 pathway [117]. Loss of miRNA-124 expression was found in neurons in the perilesion area of mice with an SCI [118]. However, the inflammatory response could be reduced by affecting the transcriptome of local macrophages or microglia by administering miR-124 in SCI rat models [119]. Notably, cell therapy, including cell transplantation and stimulating potential stem cell differentiation, is a potential SCI treatment [120, 121].

The role of miR-124 in SCI cell therapy has also been studied. MiR-124 regulates the differentiation of bone marrow-derived mesenchymal stem cells into neurons, promoting critical SCI repairs [122, 123]. In epilepsy, the role of miR-124 seems to be double-edged; miR-124 can effectively attenuate epileptogenesis *via* a neuron restrictive silencer factor, but it also augments microglia activation and inflammatory cytokines, through which epilepsy is promoted [124]. MiR-124 is downregulated in GBM tissue; this promotes the growth and invasiveness of GBM cells [125] and indicates

poor prognoses in glioma patients [126]. Several studies have shown that miR-124 can inhibit the proliferation, migration, and invasion of glioma cells [127, 128]. By directly targeting miR-124, circular matrix metallopeptidase 9 (circMMP9), an oncogene, accelerates GBM cell proliferation, migration, invasion, and tumorigenesis [129]. Although the regulatory effects of melatonin on miR-124 need further study, the above information coupled with melatonin's wide-ranging effects is an exciting prospect, and miR-124 may play an important role in the mechanisms of melatonin treatment in various CNS diseases.

9.3. Melatonin and microRNA-146

MiR-146a was previously found to be transcriptionally induced by NF-κB and to control TLR and cytokine signaling through a negative feedback regulatory loop involving the downregulation of interleukin- (IL-) 1 receptor-related kinase 1 and tumor necrosis factor (TNF) receptor-related factor 6 protein levels [130]. This suggests a close relationship between miR-146 and inflammation. MiR-146a/b inhibits the intensity and duration of endothelial activation in response to proinflammatory cytokine stimulation; miR-146a overexpression represses endothelial activation and leukocyte recruitment by IL-1β treatment, and knockdown of miR-146a/b *in vitro* has an opposite effect. These effects may be related to the ability of inhibiting NF-κB [131].

Currently, there are few studies about miR-146 in CNS diseases, but it is worth noting that many of these diseases, including stroke, TBI, and AD, share a common pathological process: inflammation. Furthermore, it is generally believed that miR-146 is involved in inflammation regulation. Therefore, as a substance that has been shown to have anti-inflammatory properties in many studies, the relationship between melatonin and miR-146 is worth studying. Carloni *et al.* found that miR-146a expression was significantly decreased in lipopolysaccharide (LPS)-induced neonatal brain inflammation associated with an increased expression of IL-1; this effect could be completely blocked by or treated with melatonin [60]. In addition, melatonin has been shown to negatively modulate NF-κB [132, 133], similar to the effects of miR-146; this suggests a novel possible mechanism. Epilepsy and stroke are also associated with miR-146, providing a basis for melatonin to be used in these diseases.

9.4. Melatonin and microRNA-16

Circulating miR-16 can be used to diagnose a hyperacute cerebral infarction with high sensitivity and specificity since miR-16 is involved in several biological processes and signaling pathways after such an infarction [134]. MiR-16 is a post-transcriptional regulator of Aβ precursor protein (APP); overexpression of this miRNA *in vitro* and in *vivo* can downregulate APP in senescence-accelerated mouse prone strain 8 (SAMP8) mice, a model of early-onset AD [135]. In addition, Yang *et al.* found miR-16 is most strongly correlated with malignancy in nearly all analyzed human tumors [136]. Moreover, many studies have shown that miR-16 is closely related to glioma. Upregulating the expression of miR-16 by different methods can inhibit the proliferation of glioma cells by promoting glioma cell apoptosis [137]. By inhibiting BCL2 and the NF-κB1/MMP-9 signaling pathway, miR-16 inhibits glioma cell growth and invasion [136]. Notably, NF-κB can also be inhibited by melatonin in many diseases [80]. Furthermore, miR-16 is regulated by melatonin, mediates melatonin-induced cell growth, and functions by targeting cyclin D1 in spermatogenesis [138]. Combined with the above, it is reasonable to speculate that the regulation of melatonin on miR-16 may play a key role in the treatment of various CNS diseases.

9.5. Melatonin and microRNA-34

MiR-34a was originally thought to be a tumor suppressor gene that inhibits SIRT1 [139]. By inhibiting SIRT1, miR-34a increases the acetylation and transcription of p53, leading to the induction of pro-apoptotic genes [140]. Melatonin has been found to be involved in regulating SIRT1 expression in many CNS diseases. By activating SIRT1 signaling, melatonin treatment exerts a profound cerebral protective [141] effect against ischemic stroke [142]. Melatonin treatment also rescues hippocampal neurons against LPS-induced oxidative stress damage, acute neuroinflammation, and apoptotic neurodegeneration *via* SIRT1 signaling pathway activation [143]. Early brain injury following SAH can be repressed by melatonin through the Sirt1/NF-κB signaling pathway [144]. Carloni *et al.* found that melatonin completely reversed the effect of ischemic stroke on SIRT1, and this was associated with a reduction in necrotic cell death and activation of the intrinsic apoptotic pathway [145]. Importantly, in different pathological conditions, especially in tumors and non-tumor diseases, melatonin exerts complicated effects on SIRT1 that may create the opposite outcome. Although the underlying mechanism still needs further study, current evidence suggests that miR-34a plays an important role in the regulation of Sirt1 by melatonin. In addition, miR-34a expression was significantly increased after LPS administration, whereas pretreatment with melatonin reduced its expression [60]. Correspondingly, Sirt1 expression decreased after LPS treatment and the effect was reversed significantly by melatonin. Given the above mechanism, melatonin plays an anti-inflammatory role in neonatal brain inflammation.

9.6. Melatonin and microRNA-155

Ling *et al.* demonstrated that miR-155 is markedly upregulated in several glioma cell lines and human glioma samples; also, it can down-regulate the expression of FOXO3a to enhance the proliferation and invasion ability of glioma cells, which indicates that silencing miR-155 expression may be a new strategy for treating human gliomas [146]. In subsequent experiments, the authors used melatonin to treat glioma cell lines and found that melatonin can reduce the expression of miR-155 in glioma by inhibiting c-MYB, and repressing the migration, invasion, and proliferation of tumor cells [16]. Together with miR-128a and miR-516a-3p, miR-155 is also significantly elevated in sporadic pituitary adenomas [147]. Melatonin can significantly suppress pituitary tumor growth *in vitro* [132]; this result implies a potential mechanism of melatonin to treat pituitary tumors.

MiR-155 is also involved in macrophage polarization; it is the most highly upregulated miRNA in LPS/interferon-γ-treated macrophages [148-150]. Through the CCAAT/

enhancer binding protein signaling cascade, miR-155 promotes M1 macrophage polarization. Therefore, melatonin may inhibit miR-155 expression by regulating c-MYB, thereby reducing M1 macrophage differentiation [151]. Microglia, the resident macrophages in the CNS, also have two phenotypes: M1 (pro-inflammatory) and M2 (anti-inflammatory) [152]. In many diseases, including stroke, TBI, ALS, and AD [153-155], microglia differentiation has been linked to miR-155 alterations. Experimental results suggest that melatonin can reduce the M1 phenotype, thus, playing a protective role in neuroinflammation; this also suggests a possible role of miR-155 in microglial polarization. Butovsky *et al.* found similar results. In their study, genetic miR-155 ablation delayed the onset of ALS and prolonged mouse survival. The potential mechanism is closely related to that of reduction in M1 microglial differentiation [153]. The above results suggest that melatonin can play a therapeutic role by regulating miR-155, an important target in a variety of CNS diseases.

9.7. Melatonin and microRNA-132

MiR-132 is a brain-enriched miRNA that is involved in the pathological processes of AD. The miR-132 expression is significantly down-regulated in human AD brains and in an AD mouse model that overexpresses Aβ or tau [156]. An miR-132 deficiency exacerbates the pathologies of Aβ and tau [157]. Melatonin can protect neurons against Aβ-induced neurotoxicity, enhance neuronal viability and reduce ROS levels. These effects are related to an increase in miR-132 *via* melatonin that was previously downregulated by Aβ. Overexpression of miR-132 could also markedly increase cell viability during Aβ exposure. In addition, melatonin treatment can reduce PTEN and FOXO3a, which are significantly increased after exposure to Aβ25-35 [71].

Research of miR-132 in CNS diseases has also been widely performed. The plasma miR-132 levels in PD were shown to be significantly elevated [158]. It has not yet been determined whether this increase of expression is due to the pathological process of the disease itself or to the compensatory elevation of the process. In stroke studies, the neuroprotective effect of miR-132 was also verified [159]. MiR-132 decreased the infarct volume, reduced blood-brain barrier (BBB) permeability, and improved the behavioral function of mice after a middle cerebral artery occlusion by directly suppressing MMP-9 expression, reducing the degradation of the tight junction proteins vascular endothelial cadherin and β-catenin, thus, maintaining BBB integrity [160]. In ICH, miR-132 also attenuates neurobehavioral and neuropathological changes through a similar mechanism [161].

A delayed inflammatory response is closely associated with SCI severity *via* elevated miR-132, though notoginsenoside R1 could guard neuronal cells from LPS-triggered inflammatory damage [162]. Nonetheless, the role of miR-132 remains controversial in epilepsy-related studies. MiR-132 silencing suppresses spontaneous seizures; the possible mechanism may be related to the inhibition of the mossy fiber sprouting-CA3 pathway following miR-132 silencing [163] or through the miR-132/p250GAP/Cdc42 pathway by regulating the morphology and electrophysiology of dendritic spines [164]. However, it was also suggested that miR-132 promotes epileptogenesis by regulating brain-derived neurotrophic factor/TrkB signaling in hippocampal neurons [165]. Notably, melatonin regulation of the PTEN/AKT/FOXO3a signaling pathway, an aforementioned miR-132 pathway, has also been verified [166]. These results highly suggest that the relationship between melatonin and miR-132 plays an important role in many pathological environments.

9.8. Melatonin, the long non-coding RNA-H19/microRNA-675 axis, and microRNA-let-7a

H19 RNA is one of the most highly abundant and conserved transcripts in mammalian development [167]. MiRNA-675 was considered to be a derivative of H19 RNA [168]. In the study by Yang *et al.*, melatonin was shown to affect H19 levels by influencing the H19 promoter transcription efficiency that, in turn, alters the expression of miR-675, a negative regulator of P53. P53 is a known key tumor suppressor that controls the apoptosis of cells [169]. Although there have been many studies about the therapeutic effects of melatonin on early brain injury after SAH [77], the above mechanism undoubtedly expands the underlying targets of melatonin and opens new avenues for research.

The regulatory function of melatonin on H19-miR-675 was also confirmed in pulmonary hypertension [170]. However, in glioma tissue, studies have revealed an H19 overexpression that is positively associated with the tumor grade and negatively associated with patient survival [171]. It was suggested that H19 promotes glioma cell proliferation, mediated by miR-675 [172]. Considering the distinct pathophysiological conditions of tumor cells and non-tumor cells, it is difficult to determine whether melatonin will aggravate the proliferation of glioma cells through this mechanism. However, melatonin is currently considered to have a therapeutic effect on glioma [173], attributed to its multi-target effect in the overall environment. In Song's study, altered miR-let-7a expression was found after SAH and was suggested to be negatively regulated by H19. Their experimental results demonstrate that miR-let-7a has an inhibitory effect on NGF. The protective effect of melatonin after SAH is likely achieved by reducing apoptosis *via* the miR-let-7a-associated pathway since NGF is an important regulator of apoptosis [174]. In addition, miR-let-7 released from injured neurons and immune cells can aggravate neuroinflammation; thus, neuroprotective effects can be achieved by reducing miR-let-7 expression [175]. MiR-let-7 has also been explored in CNS malignancies. It is associated with glioma grades and patient outcomes; furthermore, it can induce glioma cell apoptosis and inhibit cell growth through the K-RAS pathway [176].

9.9. Melatonin and circular RNA

CircRNAs comprise a large class of ncRNAs produced by a non-canonical splicing event called backsplicing [177]. In recent years, high-throughput RNA sequencing (RNA-seq) and circRNA-specific bioinformatics algorithms have identified thousands of circRNAs with tissue-specific expression patterns [178, 179] Studies have also found a variety of biological functions for circRNA, including serving as miRNA sponges and protein scaffolding, interacting with and enhancing protein function, and influencing the process of protein recruitment [179]. Previous studies have detected

numerous distinct circRNA spatiotemporal expression patterns in brain samples [180], indicating circRNA may have specific functions in the CNS. Similar to microRNA and lncRNA, circRNA can be used as a potential biomarker for the diagnosis and prognosis of CNS diseases. In addition, through these biological functions, circRNA is likely to be involved in the pathological processes of many CNS diseases [181].

CircRNA ciRS-7 (Cdr1as) is one of the most studied circRNAs in the CNS. Cdr1as functions as a sponge for miR-7a, and promotes ischemic cell death and tumorigenesis by depleting the cell-protective miR-7a [182]. A total of 521 circRNAs displayed significant differential expression profiles of peripheral blood mononuclear cells from patients with acute ischemic stroke compared with healthy volunteers, including 373 upregulated and 148 downregulated circRNAs [183]. Other studies further validated the importance of circRNA in ischemic stroke. For example, circHECTD1 can regulate astrocyte activation by targeting the miR142-TCDD-inducible poly-ADP-ribose polymerase (TIPARP) pathway *via* autophagy regulation after a stroke [184]. Moreover, in ischemic stroke, circTLK1 aggravates neuronal injury and neurological deficits *via* the miR-335-3p/TIPARP signaling pathway [185].

CircRNA KIAA1586 was identified as a key risk factor involved in AD pathogenesis [186]. Recently, using two large brain-derived RNA-seq datasets, Dube *et al.* demonstrated that

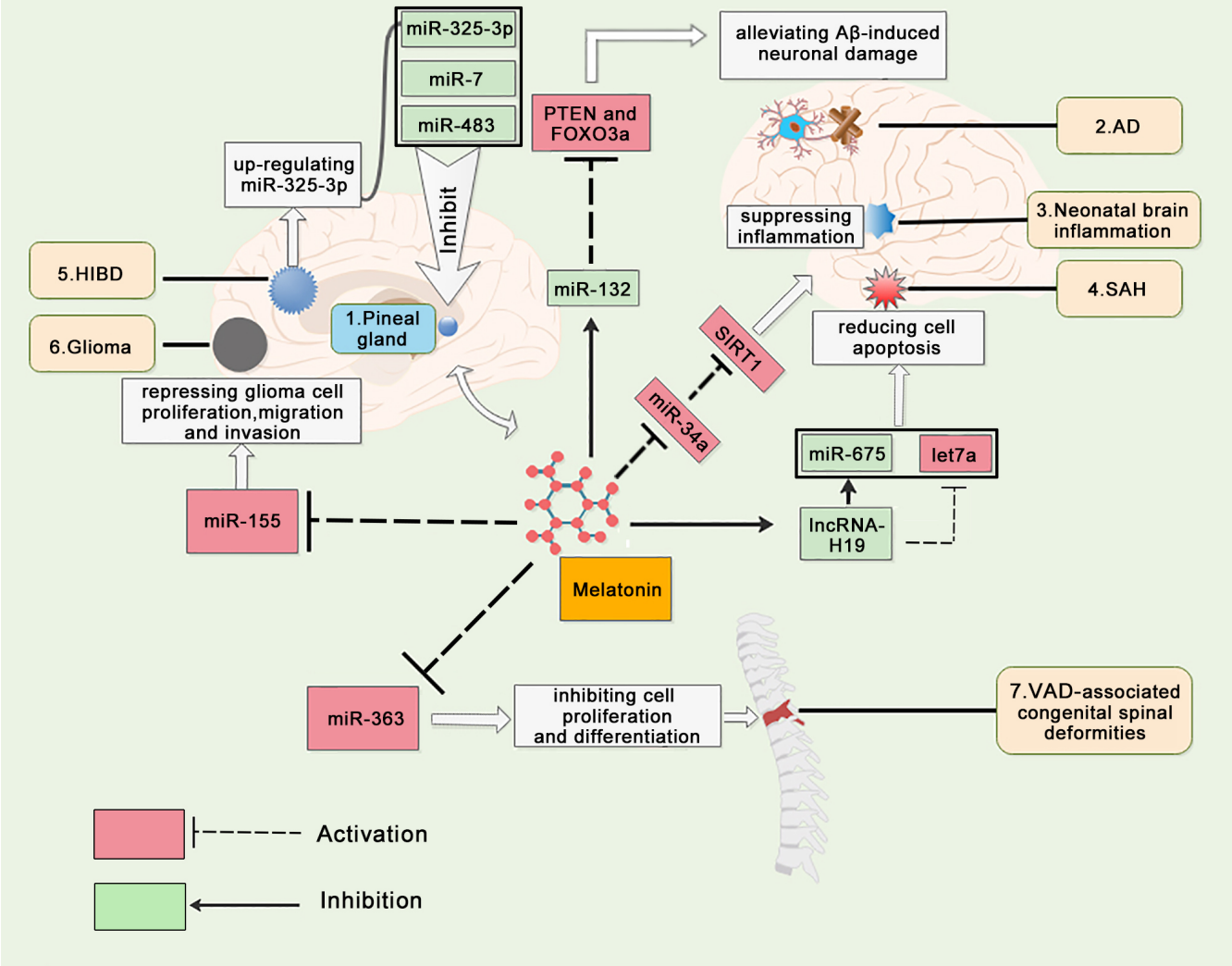

Fig. (1). Non-coding RNA related to melatonin has been reported in CNS diseases. (1) miR-325-3p, miR-7, and miR-483 inhibit melatonin synthesis. (2) Melatonin rescues the Aβ-induced neurotoxicity *via* the miR-132/PTEN/AKT/FOXO3a pathway. (3) Melatonin represses neonatal brain inflammation by reducing the expression of miR-34a *via* SIRT1 regulation. (4) The H19-miR-675-P53-apoptosis and H19-let-7a-NGF-apoptosis signaling pathways are involved in the brain injury regulatory process after SAH. (5) The expression of AANAT, a key regulator for melatonin synthesis, is severely reduced in the pineal gland post HIBD. (6) Melatonin inhibits the miR-155 expression and, thereby, represses glioma cell proliferation, migration, and invasion. (7) Melatonin rescues the inhibitory effects of miR-363 on neural stem cell (NSC) proliferation and neuronal differentiation in vitamin A deficiency- (VAD-) associated congenital spinal deformities. Abbreviations: Aβ, amyloid beta; AD, Alzheimer's disease; AKT, protein kinase B; CNS, central nervous system; FOXO3a, forkhead box O3; HIBD, hypoxic-ischemic brain damage; miR, micro ribonucleic acid; PTEN, phosphatase and tensin homolog; SAH, subarachnoid hemorrhage; SIRT1, sirtuin-1. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

alterations in circRNAs are a reproducible phenomenon in AD and that circRNA expression levels significantly correlate with AD severity [187]. Alterations in circRNA expression profiles are also found in the injured cerebral cortex after TBI [188, 189]. Although these findings suggest that circRNA has value in the diagnosis and therapy of CNS diseases, it is crucial to further verify and discover circRNAs closely related to CNS diseases based on RNA-seq results. Accurate identification with high sensitivity of circRNAs, specifically dysregulated in disease situations, is needed for future clinical development [190].

Unfortunately, there are few reports about the relationship between melatonin and circRNA. However, current research findings have revealed circRNA to have a wide range of biological effects. Pathological processes such as inflammation, oxidative stress, and cell death that are present in many diseases may serve as regulatory targets of circRNA [191, 192]. Considering the multi-target characteristics of melatonin, future research should consider these mechanisms to explore its regulatory role regarding circRNA. Moreover, miR-7 is a target for Cdr1as as the ciRS-7/miR7 axis has been suggested to play an important role in a variety of cancers [193, 194]. As mentioned previously, miR-7 is involved in the synthesis of melatonin; hence, whether ciRS-7 is also involved in melatonin synthesis requires further study.

PERSPECTIVE AND CONCLUSION

Here, we summarized the possible role of melatonin and ncRNA in CNS diseases based on recent research on CNS disorders (Fig. **1**). Various microRNAs such as miR-325-3p, miR-7, miR-483, and miR-325-3p can affect melatonin's synthesis. This process may be one of the pathological mechanisms of CNS diseases. This also means that ncRNAs can be used as a treatment target by altering melatonin levels. In specific diseases, such as AD, melatonin can exert a neuroprotective effect in Aβ-induced neuronal damage *via* the miR-132/PTEN/AKT/FOXO3a pathway. By inhibiting miR-34a, melatonin can downregulate SIRT1, a negative molecular regulator of the inflammatory response, thus modulating neonatal brain inflammation. In SAH, lncRNA-H19 is an important ncRNA, which can affect the expression of miR-675 and let-7a to suppress cell apoptosis. There are many ncRNAs related to glioma. Among them, miR-155 is related to melatonin, which represses tumor cell proliferation and migration through miR-155 regulation. miR-363 can inhibit cell proliferation and differentiation in VAD-associated congenital spinal deformities, while melatonin inhibits miR-363 alleviating this process.

Our understanding of the biological properties and functions of ncRNAs is constantly increasing with the evolution of genomics technologies. NcRNAs can be used as a biomarker for many diseases, and further research will aid early screening and diagnosis of a variety of diseases. This could prove especially useful for diseases in which early symptoms are not obvious, such as AD, considering that pathological processes are often detectable before the onset of symptoms. A comprehensive exploration of ncRNAs associated with such diseases could bring significant benefits. The current problem lies in how to better translate the findings from preclinical experiments into clinical applications; this may require multi-center, large sample validation to rule out false-positive results.

As the biological functions of ncRNAs are gradually unveiled, the concept of treating disease by modulating ncRNA function has also been proven. Melatonin could be an important form of treatment. Exploring its mechanism of action is critical for expanding its potential clinical applications. Through its interactions with ncRNAs, melatonin can affect some common pathological mechanisms, including inflammation, cell death, and oxidative stress injury, thus, playing a crucial role in CNS diseases. In addition, ncRNA is also involved in melatonin synthesis, which is increased in many pathological conditions. Current research on melatonin and ncRNA is predominantly focused on miRNA. Although there are many mechanisms through which melatonin can regulate miRNAs, some questions remain. For example, among the many miRNAs that can be regulated by melatonin, how can we identify those, which are important in a specific disease process? The widespread popularity of high-throughput sequencing technology and CRISPER/Cas9 will help to solve these problems. Furthermore, some miRNAs are differentially expressed in tumor cells and non-tumor cells; what are the mechanisms involved in these differences? In addition to focusing on miRNAs, future research should also examine lncRNAs and circRNAs. More importantly, it is worth noting that most of the current research using ncRNA for treatment is mainly preclinical research. Although great progress has been made, the key issues like safety, reliability, dose, route and time window of administration of ncRNA require a lot of clinical research to further explore. For example, the previous study has found cardiac AAV6-miR-199a delivery could reduce infarct size and cardiac fibrosis as well as improve contractile function in acute myocardial infarction pigs whereas uncontrolled, long-term expression of miR-199a would finally induce sudden cardiac death of most animals [195]. In conclusion, recent research has strengthened the evidence of the links between melatonin, ncRNAs, and CNS diseases. Further research into the mechanisms that govern these links could open new therapeutic avenues for the treatment of CNS diseases.

LIST OF ABBREVIATIONS

AANAT	=	Aralkylamine N-acetyltransferase
AD	=	Alzheimer's disease
ALS	=	Amyotrophic lateral sclerosis
APP	=	A β precursor protein
Aβ	=	Amyloid beta
BBB	=	Blood-brain barrier
Bcl2	=	B-cell lymphoma 2
Cdr1as	=	CircRNA ciRS-7
ceRNA	=	Competing endogenous RNA
circRNA	=	Circular RNA
c-MYB	=	C-myeloblastosis
CNS	=	Central nervous system
CPCs	=	Cardiac progenitor cells

CSF	=	Cerebrospinal fluid
EAE	=	Experimental autoimmune encephalomyelitis
FOXO3a	=	Forkhead box O3
GBM	=	Glioblastoma
GSDMD	=	Gasdermin D
I/R	=	Ischemia-reperfusion
ICH	=	Intracerebral hemorrhage
IL-1β	=	Interleukin-1 beta
JAK	=	Janus kinase
JNK	=	Jun N-terminal Kinases
lncRNA	=	Long non-coding RNA
LPS	=	Lipopolysaccharide
MAPK	=	Mitogen-activated protein kinase
MEG3	=	Maternally expressed 3
miRNA	=	MicroRNA
MMP9	=	matrix metallopeptidase 9
mRNA	=	Messenger RNA
ncRNA	=	Non-coding RNA
NF-κB	=	Nuclear factor-kappaB
NGF	=	Neural growth factor
NLRP3	=	Nucleotide-binding domain leucine-rich repeats family protein 3
PD	=	Parkinson's disease
PI3K/Akt	=	Phosphoinositide 3-kinase/protein kinase B
PTEN	=	Phosphatase and tensin homolog
RNA	=	Ribonucleic acid
ROS	=	Reactive oxygen species
SAH	=	Subarachnoid hemorrhage
SCI	=	Spinal cord injuries
SIRT1	=	Sirtuin-1
STAT	=	Signal transducer and activator of transcription
TBI	=	Traumatic brain injury
TIPARP	=	TCDD-inducible poly-ADP-ribose polymerase
TLR	=	Toll-like receptor
VDACs	=	Voltage-dependent anion channel proteins

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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