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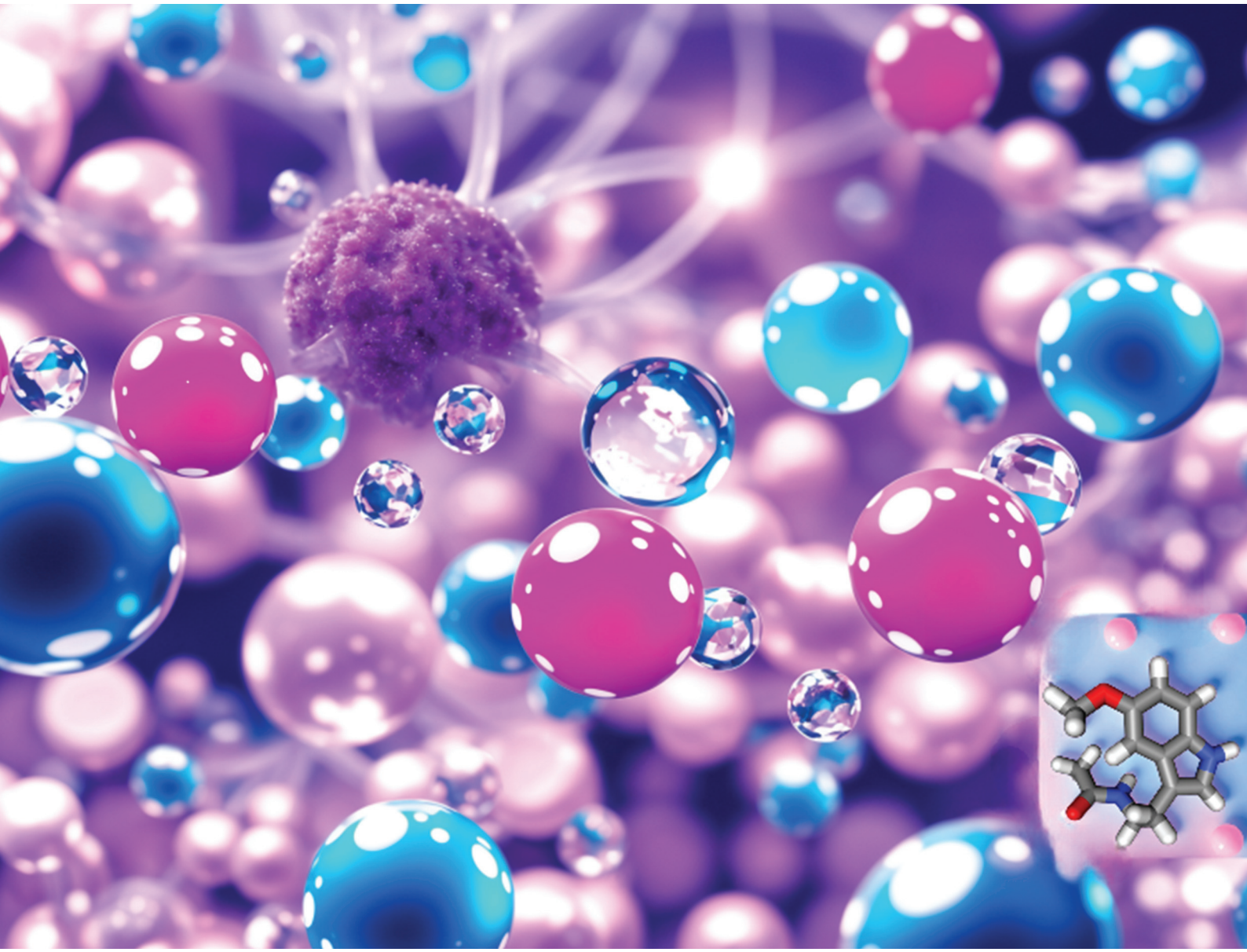

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Melatonin and the nervous system: nanomedicine perspectives

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The mechanism of action of melatonin on the nervous system, sleep, cognitive deficits, and aging is not fully understood. Neurodegenerative diseases (ND) are one of the leading causes of disability and mortality worldwide. Sleeping and cognitive impairments also represent common and serious public health problems, particularly deteriorating with the aging process. Melatonin, as a neuromodulatory hormone, regulates circadian rhythms and the sleep–wake cycle, with functions extending to antioxidant, anti-inflammatory, neuroprotective, and anti-aging properties. However, melatonin is a hydrophobic compound with relatively low water solubility and a short half-life. While melatonin can cross the blood–brain barrier, exogenous melatonin administered orally or intravenously has poor bioavailability, undergoes rapid metabolism in the circulation, and shows limited brain accumulation, ultimately compromising its therapeutic efficacy. In recent years, the convergence of melatonin research with nanomedicine ensures safe therapeutic uses, limited drug degradation, and perspectives for targeted drug delivery to the central nervous system. Here we outline the promising neurotherapeutic properties of nanomaterials as carriers loaded with melatonin drug alone or in combinations with other active molecules.

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1 Introduction

Neurodegenerative pathologies and cognitive damage represent common and serious public health problems. Over the past three decades, there has been a significant increase globally in the prevalence of neurological conditions such as stroke, Alzheimer's disease (AD), dementia, and meningitis attributed to factors like population aging and growth and heightened exposure to environmental, metabolic, and lifestyle risk factors. According to the latest analysis done by the 2021 Global Burden of Disease, Injuries, and Risk Factors Study, 37 neurological conditions (ranked as the leading cause of disability-adjusted life-years worldwide) affected 3.4 billion individuals and caused the death of 11.1 million people in 2021. Disorders affecting the nervous system are diverse and include neurodevelopmental disorders, late-life neurodegeneration, and newly emergent conditions, such as cognitive impairment following COVID-19.[1] Aging is often associated with increasing impaired brain homeostasis and represents a major risk factor for most neurodegenerative disorders.

An age-related decline of melatonin (MT) disrupting mitochondrial homeostasis and cytosolic DNA-mediated inflammatory reactions in neurons is the main contributory factor in the emergence of neurological abnormalities.[2] In addition, the circadian clock exerts a notable influence on neurons during both developmental stages and throughout aging processes.[3] The suprachiasmatic nucleus (SCN), located in the hypothalamus, is the principal circadian clock of the brain.[4] Circadian rhythms (around 24 hours) significantly influence human lives, particularly through the sleep–wake cycle. Nearly all essential physiological functions and metabolic processes are regulated by circadian rhythms.[5] Growing evidence reveals a bidirectional link between disturbances in circadian rhythms, sleep patterns, and neurodegenerative diseases (ND). Circadian disruptions and sleep disorders exacerbate neurodegeneration, and conversely, ND can disrupt circadian rhythms and sleep.[6] Standard aging is associated with a reduced ability to initiate and maintain sleep. Sleep disruption beyond normal aging is especially prevalent in dementia as disrupted sleep is common in people with ND.[7] The neuroprotective potential of MT to influence the connections between sleep disturbances, aging, and neurological conditions has not been fully exploited yet.

MT is a neuro-regulatory hormone that is essential for circadian rhythm. In humans, serum MT levels remain low during the daytime (10–20 pg mL^{-1}). Around 10:00 PM, MT secretion increases significantly, rising continuously over 4 hours and reaching its peak concentration (80–120 pg mL^{-1}) between

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2:00 and 4:00 am. Thereafter, MT levels gradually decline, returning to the lower baseline concentrations observed during the daytime.[8] The release of the endogenous hormone MT from the pineal gland progressively diminishes with aging and individuals with neurological disorders tend to have reduced levels of MT.[9,10] MT is known for its preventive and therapeutic effects across a wide range of diseases including neurodegenerative disorders, aging, depression, and ocular, cardiac, immune, and orthopedic diseases.[11–13] The susceptibility of people to these diseases increases with age, particularly neurological disorders. The brain is especially vulnerable to the detrimental effects of reactive oxygen species (ROS) due to its relatively high consumption of oxygen, elevated metabolic rate, excessive amount of iron, high content of polyunsaturated fatty acids, and comparatively limited ability for cellular regeneration when compared with other organs.[14,15]

The role of MT in various neurological disorders in *in vitro* or *in vivo* models is summarized in Table 1. In both short-term paradigms (24 to 72 hours) and long-term treatments (23 days to 9 months) in animal models, MT exhibits good therapeutic effects in some neurological disorders. Single-dose or short-term administration alleviates oxidative stress, inflammation, and cognitive deficits, as observed in 24-hour MCAO-mediated acute ischemic stroke[16] and sleep deprivation models.[17] In contrast, long-term MT treatment supports neuroprotection, mitigates neurodegeneration, and enhances hippocampal neurogenesis in aging-related and chronic disease models such as Alzheimer's[18] and multiple sclerosis.[19] MT exerts its therapeutic and neuroprotective effects through multiple mechanisms such as (i) downregulating inflammatory factors, (ii) inhibiting cell apoptosis, (iii) modulating signal transduction and gene expression, (iv) regulating enzyme and neurotrophic protein levels, (v) restoring the function of mitochondria and endoplasmic reticulum (ER), (vi) reducing oxidative stress, and (vii) maintaining circadian rhythms.

MT is traditionally administered orally, but its bioavailability is limited due to its poor oral absorption, short biological half-life, and extensive first-pass metabolism.[20] The oral transmucosal pathway resulted in high MT plasma concentrations, possibly due to avoiding the first-pass effect. Subcutaneous injection of free MT drug displayed a rapid absorption rate but showed no advantages compared with other administration routes. Transdermal delivery of MT was used in local applications requiring slow absorption and deposition in the skin.[21] Limited MT absorption on mucosal and dermal surfaces hampered its efficient use as an antioxidant and neuroprotective compound. Overall, conventional approaches have failed to achieve appropriate pharmacokinetic and pharmacodynamic properties of MT at the target site, and thus produced low therapeutic efficacy and often elevated toxicity.[21] The blood–brain barrier (BBB) is composed of brain capillary endothelium and effectively prevents over 98% of all small-molecule drugs and 100% of large-molecule neurotherapeutics from entering the brain.[22] The presence of the BBB poses a unique challenge to the accessibility of drugs and antioxidants to the central nervous system (CNS), preventing them from effectively reaching therapeutic concentrations.[23,24]

Novel nanotechnologies exploiting the intranasal route are considered promising strategies for MT delivery to the brain.[32,33] Nano-drug delivery systems effectively protect bioactive agents from degradation in physiological conditions while ensuring controlled release, prolonged efficacy, and further reduced side effects.[34] MT-loaded nanocarriers have exhibited superior antioxidant, anti-inflammatory, and antitumor properties across different cell types and tissues compared with the free MT drug.[35–37] A variety of nanocarriers, including solid lipid nanoparticles (SLNs), polymeric vesicles, silica nanoparticles (NPs), nanofibers, graphene-based nanocarriers, and metallic or non-metallic NPs, have been engineered to overcome MT's challenges such as poor solubility, stability, and bioavailability, enabling sustained delivery in some systems.[38] Considering the vital functions of the nervous system, this review focuses on the nanocarrier-mediated delivery of MT to the brain and its application in treating and improving neurological disorders.

2 Neuroprotective and neuro-repairing effects of melatonin

Although every neurodegenerative disease exhibits unique molecular mechanisms and clinical characteristics, there are commonly recognized pathways across the various pathological processes. These pathways include protein misfolding and aggregation, oxidative stress, mitochondrial dysfunction, impaired phosphorylation, and dysregulation of metal homeostasis that often occur concurrently.[39] MT shows a regulatory effect on the pathological processes through receptor-dependent and receptor-independent pathways (Fig. 1). By the receptor-independent pathway, MT can upregulate antioxidant defense mechanisms, directly remove ROS, inhibit inflammation, and prevent apoptosis. At physiological concentrations, MT exerts receptor-mediated actions, whereas receptor-independent actions usually require supra-physiological concentrations.

There are four different MT receptor subtypes. Two of them are membrane-associated receptors, while the other two are nuclear receptors. Melatonin receptor 1 (MT1) and melatonin receptor 2 (MT2) subtypes are present in humans and other mammals. Melatonin receptor 3 (MT3) is a cytosolic enzyme known as quinone reductase 2 (QR2) rather than a membrane receptor. MT is also a ligand for retinoid orphan nuclear hormone receptors, referred to as ROR and RZR, at concentrations in the low nanomolar range. Both receptors are present in the central and peripheral nervous system and have been associated with cell differentiation and immune response regulation.[40]

2.1 MT1/MT2 receptor-dependent pathways of melatonin

Among the various molecular mechanisms of MT action, its most potent mechanism involves the activation of G protein-coupled receptors. These receptors, namely ML1 with high affinity and ML2 with low affinity, are now known as MT1 and

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Table 1 Therapeutic and functional roles of melatonin in various *in vitro* or *in vivo* models of neurological disorders

Disease	*In vitro*/*in vivo* model	ROA/dose[a]	Effects	Year/ref.
Alzheimer's disease (AD)	*In vitro*: amyloid-β (Aβ)-induced inflammation in SH–SY5Y cells	10 μM	MT played a protective role against Aβ–induced inflammation *via* an inflammasome–associated mechanism that is essential in inducing the active forms of cytokines and pyroptosis.	2023[25]
Aging-related AD	*In vivo*: SAMP8 mice	10 mg mL^{-1} kg^{-1} oral, 9 months	Chronic treatment with MT for 9 months decreased the neurodegenerative processes and the neurodegeneration-induced neurogenic response. MT induced recovery in the functionality of adult hippocampal neurogenesis in aged SAMP8 mice.	2022[18]
Parkinson's disease (PD)	*In vitro*: (MPP+)-toxin-induced model in SH-SY5Y cells	10 μg mL^{-1} in culture medium	MT showed promoting anti-oxidative and anti-apoptotic properties (increased SOD and GSH-Px activity, Bcl2 levels, and decreased ROS, MDA, Bax, and cleaved caspase-3 levels). MT hindered the toxic effects of MPP+ on dopaminergic neuronal cells *via* upregulation of the HSF1/HSP70 pathway, which could be a promising therapeutic strategy for PD.	2022[26]
Japanese encephalitis virus (JEV) infection	*In vitro*: SH–SY5Y cells	125–500 μM in culture medium	MT interfered with the replication cycle of JEV; abrogated the enzymatic function of the nonstructural proteins (NS3 and NS5); attenuated the JEV-induced upregulation of inflammatory factors (TNF-α, TLRs, NF-κB, and COX-2); and reduced the pro-apoptotic proteins levels and the caspase cascade activity.	2023[27]
Cervical spondylotic myelopathy	*In vitro*: primary cultures of rat cortical neurons, SH-SY5Y cells. *In vivo*: a rat model of chronic cervical cord compression	10 mg kg^{-1} (i.p.)	MT attenuated protein kinase R-like ER kinase–eukaryotic initiation factor 2α-C/EBP-homologous protein, inositol requiring enzyme 1, and transcription factor 6 signaling pathways to release ER stress and prevents Bax translocation to the mitochondrion. MT remodeled the ER morphology and restored homeostasis *via* ER-phagy (by activation of Sec. 62 receptor) in injured neurons.	2023[28]
Huntington's disease (HD)	*In vitro*: N2a cells, Q7 and Q111 knockin mouse striatal cells. *In vivo*: AANAT knockout mice	5 μM in culture medium	Insufficient MT levels impaired mitochondrial homeostasis resulting in mitochondrial DNA (mtDNA) release and activation of the cytosolic DNA-mediated inflammatory response in neurons. Exogenous MT inhibited the increased mtDNA release, cGAS activation, and inflammation in an HD mouse model.	2020[29]
Ischemic stroke	*In vivo*: rats with MCAO model	5 mg kg^{-1} (i.p.) a single dose, 24 h	MT attenuated MCAO-mediated stress associated with the MAPK p-P38/p-JNK pathways; restored the expression level of thioredoxin but did not affect the Nrf2 levels; alleviated NF-kB-induced inflammatory types (NOS-2 and COX-2). The elevated expression of p-NF-kB was accompanied by decreased thioredoxin expression.	2020[16]
Multiple sclerosis (MS)	*In vivo*: male and female mice with experimental MS induced by cuprizone	80 mg kg^{-1} day^{-1} (i.p.) 9 weeks	In the demyelination stage, MT showed neuroprotective effects in both male and female mice, improving motor ability and antioxidant levels (CAT, SOD, GPx, and GSH) and reducing MDA and inflammatory factors (IL-1β and TNF-α). In the remyelination stage, MT showed protective effects only in male mice.	2020[19]
Neuro-degeneration	*In vivo*: PCBs mediated glutamate-induced neurodegeneration in rats	5 mg kg^{-1} day^{-1} (i.p.) 30 days	MT protected the cerebral cortex from polychlorinated biphenyl (PCB)-impaired glutamate-BDNF signaling. It scavenged the ROS, decreased the NMDAR, and increased the level of CREB and BDNF leading to neuronal survival.	2015[30]
Cognitive deficits	*In vivo*: chronic sleep deprivation-induced cognitive impairment in rat	20 mg/kg day^{-1} (i.p.) 23 days	MT treatment attenuated chronic rapid eye movement sleep deprivation-induced cognitive impairment *via* regulating HDAC3-Bmal1/Clock interaction.	2023[31]
Cognitive impairment	*In vivo*: sleep-deprived rats	15 mg kg^{-1} day^{-1} (i.p.) 24/72 h	Short-term and large dose MT pre-treatment ameliorated cognitive impairment in 24 h and 72 h sleep-deprived rats. The possible mechanism may be associated with effects on oxidative stress, BDNF and CaMKII levels in the cerebral cortex (CC) and hippocampus.	2013[17]

[a] Route of administration (ROA); intraperitoneal injection (i.p.).

MT2 receptors, respectively.[41] They are members of the G protein–coupled receptor superfamily, preferentially coupling to Gi/o proteins. The MT1 and MT2 receptors have been localized to specific regions of the rodent and human nervous system, including the hippocampus, cerebellum, suprachiasmatic nucleus (SCN), and thalamus, as well as peripheral tissues. These localizations were determined by using receptor autoradiography with 2-[^{125}I] iodomelatonin, *in situ* mRNA hybridization techniques, and immunohistochemistry. The functions of the MT1 and MT2 receptors have been studied

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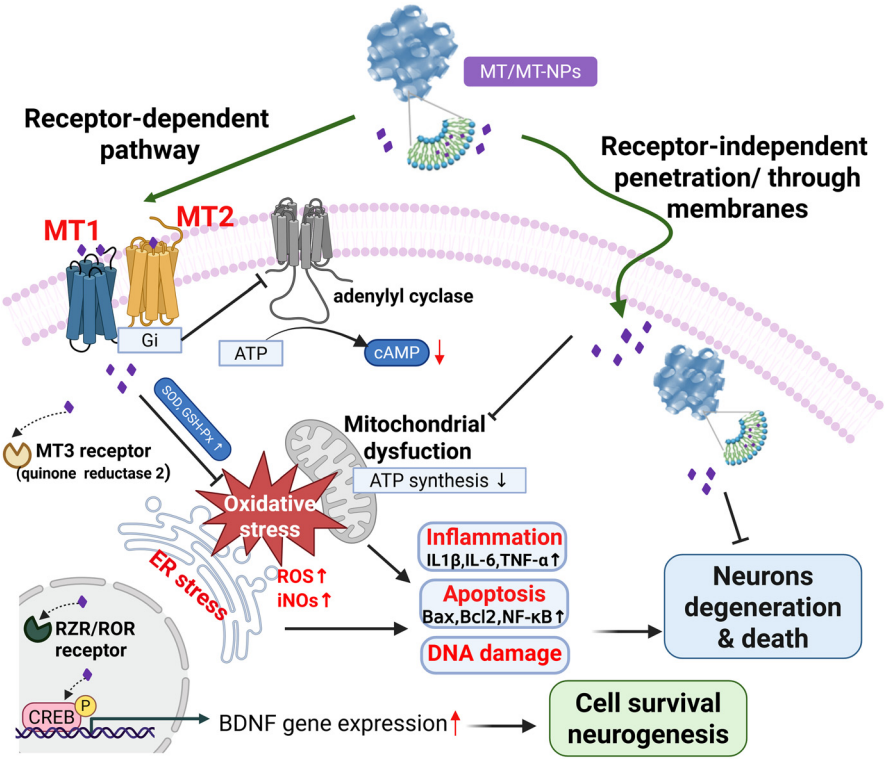

Fig. 1 Melatonin (MT) and melatonin-loaded-nanoparticles(MT and MT-NPs) can exert neuroprotective and neuro-regenerative effects through receptor-dependent and receptor-independent pathways involving the alleviation of oxidative stress, mitochondrial dysfunction, endoplasmic reticulum (ER) stress-induced inflammation, apoptosis, DNA damage, and the regulation of signal transduction and gene expression to modulate the levels of enzymes and neurotrophins such as brain-derived neurotrophic factor (BDNF) (created with *Biorender*).

through genetic deletion in mice lacking either the MT1 or MT2 receptor or through pharmacological methods using competitive MT receptor antagonists like luzindole and 4-phenyl-2-propionamidotetralin (4P-PDOT).[42]

MT receptor binding regulates several second messengers, *e.g.* cyclic adenosine monophosphate (cAMP), cyclic guanosine monophosphate (cGMP), diacylglycerol, inositol trisphosphate, arachidonic acid, and intracellular Ca^{2+} concentration ($[Ca^{2+}]$). In many cases, its effect is inhibitory and requires previous activation of the cell by a stimulatory agent.[43] Activation of the MT1 and MT2 receptors primarily triggers Gi activation, which negatively regulates adenylyl cyclase (AC), leading to lower cAMP levels and reduced activity of cAMP-dependent kinase A (PKA). Additionally, both receptors can recruit β-arrestins. MT1 activation can also initiate the Gi/PI3K/Akt, Gi/PKC/ERK1/2, and Gq/PLCβ/IP3/Ca^{2+} pathways. Activation of MT2 receptors inhibits intracellular cGMP levels, subsequently reducing the activity of cGMP-dependent kinases or protein kinase G (PKG). The signaling of MT receptors within dimeric complexes involves distinct pathways depending on the receptor pairings.[44]

MT enhances PTEN-induced putative kinase 1-dependent mitophagy *via* the MT2/Akt/NF-κB pathway, and such mitophagy is critical for high glucose-induced mitochondrial impairment and apoptosis in neuronal cells.[45] MT1 knockout led to increased loss of dopaminergic neurons and more severe motor dysfunction. It also suppressed the Sirt1/Nrf2/Ho1/Gpx4 pathway, reducing resistance to ferroptosis, and inhibited ferritin Fth1 expression, causing greater release of ferrous ions. MT1 activation prevents α-Syn-induced ferroptosis in PD, highlighting MT1's neuroprotective role in PD.[46] Copper is crucial for generating ROS induced by Aβ peptide aggregation, making copper homeostasis a potential therapeutic target for AD. Research has shown that copper chelators (tetrathiomolybdate) facilitate the non-amyloidogenic processing of Aβ protein precursor (AβPP) *via* $MT_{1/2}$/CREB-dependent signaling pathways.[47] The inducible ADAM10 production caused by copper chelators can be blocked by a melatonin receptor (MT1/2) antagonist (luzindole) and an MT2 inhibitor (4P-PDOT), suggesting that the expression of ADAM10 depends on the activation of MT1/2 signaling pathways. Furthermore, MT1 and MT2 play opposite roles in brain cancer progression. Using an MT2-selective antagonist, DH97, a study demonstrated that MT1 impairs while MT2 promotes the proliferation of glioma and medulloblastoma cell lines. It provides the first evidence of the different roles of MT1 and MT2 in brain tumor progression, highlighting their relevance as druggable targets.[48]

2.2 Role of melatonin in neurological disorders

2.2.1 Reducing oxidative stress. There has been a debate about whether oxidative stress is a cause or a consequence of

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the neurodegenerative cascade.[14] The current consensus is that an imbalance in the intracellular oxidation state represents an early event in neurodegeneration. It is increasingly recognized as a significant contributing factor to the onset and progression of neurodegenerative diseases.[49] The hypothesis has been supported by studies of animal models on the role of neuroprotective agents in the treatment of disorders associated with oxidative stress, such as stroke, traumatic brain injury, PD, and AD. However, the effectiveness of radical scavengers in reducing oxidative stress within a living biological environment is hindered by the continuous production of radicals through mechanisms like the Fenton reaction, which is catalyzed by Fe^{2+}. It has been suggested that treatment with both a radical scavenger and a Fe chelator might provide greater protection against oxidative stress in living tissue compared with treatment with either a radical scavenger or a Fe chelator alone.[50]

MT is considered a multi-pathway antioxidant and effective neuroprotective agent,[50] which demonstrates remarkable efficacy in reducing oxidative stress under various conditions through multiple mechanisms summarized as follows:

2.2.1.1 Directly neutralizing free radical scavenging activity. Unlike the classic antioxidants, MT does not display pro-oxidative behavior and has a cascade-like antioxidant potential. Any intermediates formed during its interaction with reactive species also possess free radical scavenging properties. Consequently, a single MT molecule can potentially scavenge up to four or more reactive species, enhancing its efficacy as an antioxidant.[51] For example, traditional antioxidants typically scavenge one or fewer $ABTS^{\bullet+}$ radicals and react completely within a short period (<1 min), while every molecule of MT can scavenge up to four $ABTS^{\bullet+}$ radicals with a sufficiently long reaction time (2 hours). This prolonged duration and enhanced capacity of scavenging has been attributed to the sequential generation of MT metabolites that also possess the ability to neutralize the $ABTS^{+}$ radicals.[52] The corresponding mechanism may involve multiple-electron donations *via* intermediates through a stepwise process. Intermediates including the melatoninyl cation radical, the melatoninyl neutral radical, 3-hydroxy-melatonin, and N1-AFMK appear to participate in these reactions.[53]

2.2.1.2 Indirectly regulating antioxidant enzyme activity and pro-oxidant enzyme activity. Several studies have reported that MT supplementation effectively reduces brain oxidative damage marked by decreased carbonyl, nitric oxide (NO), and malondialdehyde (MDA) content, and enhanced antioxidant enzyme activities, superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx) along with an overall antioxidant capacity.[54,55] Interestingly, an earlier study reported opposite effects, with MT treatment decreasing antioxidant enzyme levels.[56] Long-term MT administration to Alzheimer's transgenic mice reduced the expression of three antioxidant enzymes in the cerebral cortex (SOD, GPx, and CAT), suggesting decreased oxidative stress.[56] This may occur because long-term use of MT is beneficial for the restoration of normal levels of antioxidant enzymes. Under conditions of short-term oxidative stress, MT promotes the activity of antioxidant enzymes, and this represents a dynamic regulatory process.

2.2.1.3 Metal-chelating activity. MT is reported to bind transition metals involved in harmful Fenton/Haber–Weiss reactions, thus reducing the production of toxic hydroxyl radicals and subsequently lowering oxidative stress.[57] The Fenton reaction, involving divalent (Fe^{2+}) and hydrogen peroxide (H_2O_2), generates ferric iron (Fe^{3+}) and hydroxyl radicals ($^{\bullet}OH$). These radicals then react with H_2O_2, producing superoxide and further $^{\bullet}OH$ and anions in the Haber–Weiss reaction. Overall, metals like Fe, Cu, Zn, and Al catalyze the formation of highly reactive $^{\bullet}OH$ radicals through these reactions. Fenton reactions can exacerbate ferroptosis (a form of cell death induced by iron accumulation and lipid peroxidation), which is involved in the pathogenesis of PD.[46] The catalytic activities of transition metals, driven by Fenton reactions, play a role in the survival and pathological signaling pathways, neural plasticity, and neuroprotection.[58] MT and its metabolites were demonstrated to completely inhibit oxidative stress caused by Cu(II)-ascorbate mixtures through Cu(II) chelation. Similarly, MT, N1-AFMK, and 3OHM prevented the initial step of the Haber–Weiss reaction, thereby stopping $^{\bullet}OH$ production *via* the Fenton reaction. Moreover, it has been suggested that MT, alongside its known role in free-radical scavenging cascades, also participates in a concurrent 'chelating cascade', contributing to the reduction of oxidative stress.[59]

2.2.2 Regulation of mitochondrial function. The pineal gland of vertebrates produces a small percentage of the total amount of MT (possibly <5%). Extrapineal MT can be synthesized in much greater amounts in the mitochondria of all other cells. Then, it acts locally in the cellular synthesis of MT or on adjacent cells without influencing the circadian rhythms and photoperiodic environment.[60] MT is widespread but uneven distribution within cells, including high concentrations in mitochondria, likely contributes to its ability to counter oxidative stress and prevent cellular apoptosis.

Strong evidence supports MT as a mitochondria-targeted antioxidant.[61,62] MT accumulates in mitochondria at high concentrations against a gradient, probably through active transport by mitochondrial MT transporters. It protects mitochondria by scavenging ROS, inhibiting the mitochondrial permeability transition pore, and activating uncoupling proteins.[63] MT reduces the mitochondrial membrane potential, thereby inhibiting the production of superoxide anions and hydrogen peroxide. Simultaneously, it maintains the efficiency of oxidative phosphorylation and ATP synthesis, while boosting the activity of respiratory complexes, mainly complexes I, III, and IV.[64] Notably, a recent study has identified a mitochondrial GPCR mechanism contributing to the neuroprotective action of MT.[65] MT synthesized exclusively in the mitochondrial matrix activates the mitochondrial MT1 signaling pathway, which inhibits stress-induced cytochrome c release and caspase activation. Consequently, this retards the neurodegenerative process.[65]

Multiple pieces of evidence suggests that MT may cure neurological disorders by alleviating mitochondrial dysfunc-

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tion.[66] MT and related indole metabolites can reverse mitochondrial dysfunction caused by Aβ peptide aggregation. This effect is partially mediated by MT binding to plasma membrane receptors, which then activate signaling pathways to the mitochondria.[67] MT can modulate the SIRT1/Drp1 pathway, thereby ameliorating mitochondrial dysfunction, attenuating inflammation and apoptosis, and enhancing neural function after spinal cord injuries.[68]

In a study with a PD mouse model, MT displayed a protective effect against paraquat-induced motor deficits by alleviating the kinesin family member 5A-mediated axonal mitochondrial transport dysfunction in the midbrain.[69] Moreover, the application of exogenous MT boosted mitochondrial ATP production and synergy, reducing abnormal phase separation and related mitochondrial dysfunction.[70] It has been hypothesized that long-term daily MT supplementation may enhance survival, improve neurological function, and offer an alternative preventive measure against mitochondrial dysfunction after resuscitation.[71]

2.2.3 Reducing endoplasmic reticulum (ER) stress. The ER is a crucial cellular organelle that maintains cellular homeostasis by regulating calcium levels and controlling essential functions such as protein synthesis, folding, and lipid production. ER stress is the cellular response to the accumulation of misfolded proteins within the ER, which triggers a series of signaling pathways and molecular events to restore cellular balance. The accumulation and deposition of misfolded proteins within the cells are characteristic of numerous neurodegenerative diseases.[72] Post-stroke MT therapy has been shown to not only reduce mitochondrial dysfunction but also alleviate ER stress and inflammation. The effects of MT on mitochondrial and ER functions, as well as the interactions between these organelles, have highlighted their potential as therapeutic targets for stroke. In both yeast and mammals, the communication between the ER and mitochondria plays a crucial role in activating various cellular pathways, including proliferation, cell death, mitochondrial dynamics, lipid metabolism, autophagy, Ca^{2+} signaling, inflammation, mtDNA distribution, bioenergetics, and the unfolded protein response.[73]

Other studies have shown that MT is crucial in protecting neurons, improving cognitive function, and treatment of traumatic brain injury and neurodegeneration against ER stress.[74–76] C/EBP homologous protein (CHOP), also known as growth arrest- and DNA damage-inducible gene 153 (GADD153), is one of the main components of the ER stress-mediated apoptosis pathway.[77] The primary target molecule of ER stress for MT is CHOP, and PERK and GRP78/BiP are the secondary target molecules.[76] In a rat model of chronic cervical cord compression, MT reduced the activation of the signaling pathways involving PERK, eukaryotic initiation factor 2α-CHOP, inositol-requiring enzyme 1 (IRE1), and transcription factor 6 (ATF6), thereby alleviating ER stress. It also prevented Bax from translocating to the mitochondria, which supports motor recovery and protects neurons *in vivo*.

Additionally, MT can counteract ER stress-induced glutamate toxicity in primary rat cortical neurons *in vitro* and restore ER morphology and homeostasis through ER-phagy in damaged neurons.[28] SIRT1 is an NAD+-dependent histone deacetylase, and its expression is up-regulated by ER stress contributing to ER stress-induced cellular damage.[78] MT can attenuate spatial learning and memory dysfunction in developing rats by suppressing isoflurane-induced ER stress *via* the SIRT1/Mfn2/PERK signaling pathway.[79] Under oxidative stress conditions, MT treatment inhibited the activation of ER stress-related and autophagy-related proteins by promoting the upregulation of cellular prion protein expression.[80]

2.2.4 Anti-inflammatory activity. The ability of MT to modulate mitochondrial function and ER stress is closely linked to its roles in reducing inflammation, preventing apoptosis, and enhancing DNA repair. This interconnected network of actions makes MT a potent agent for maintaining neuronal health and preventing neurological diseases. MT exerts potent anti-inflammatory effects by targeting multiple molecular mechanisms. Neuroinflammatory responses are driven by several essential pro-inflammatory cytokines (IL-1β, IL-6, TNF-α), chemokines (CCL2, CCL5, CXCL1), secondary messengers such as nitric oxide (NO) and prostaglandins, and ROS. Many of these mediators are generated by *activated* resident CNS cells, including microglia and astrocytes.[81] Chronic inflammation, often linked to neurodegenerative diseases, causes pathological alterations in signaling pathways, particularly nuclear factor kappa-B (NF-κB) and signal transducer and activator of transcription 3 (STAT3). This results in increased oxidative stress and excessive production of ROS and reactive nitrogen species (RNS).[82]

Both *in vivo* and *in vitro* experiments have demonstrated that MT treatment markedly decreases hippocampal microglial activation and the expression of the inflammatory factors IL-1β and TNF-α induced by dim blue light. The beneficial effect of MT is associated with its interaction with the MT2 receptor.[83] Another mechanism involves MT binding to its specific receptor (MT1) on microglia, which activates the JAK2/STAT3 pathways and boosts the expression of telomerase in the nucleus. This leads to a reduction in the production of proinflammatory cytokines like IL-1β, TNF-α, and iNOS by M1 microglia, while enhancing the production of anti-inflammatory cytokines such as CD206 and TGFβ by M2 microglia.[84]

The Toll-like receptors (TLRs) are transmembrane signaling proteins that play a crucial role in neuroinflammation. Exogenous MT provides strong neuroprotective effects by inhibiting TLR4 activation. The activation of TLR4 triggers autophagy and apoptosis in neuronal cells, facilitates the formation of the NOD-like receptor family pyrin domain containing 3 (NLRP3) inflammasome, and elevates the secretion of downstream inflammatory cytokines.[85] The NLRP3 inflammasome is recognized as a new target for MT. This inflammasome plays a role in increasing IL-1β levels, activating caspase-1, and promoting pyroptosis.[86] Administration of a 5 mg kg^{-1} dose of MT 30 min prior to ischemia reduced brain infarction associated with sequentially rescued neuronal apoptosis. Furthermore, MT attenuated neuroinflammatory markers and ROS, induced by ischemic stroke, by halting the key players of the mitogen stress family (p38/JNK).[16]

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MT therapy has been efficient in improving cognitive and mood function in a rat model. The MT effect was dose-dependent, with lower (10–20 mg kg^{-1}) doses improving several cognitive tasks and mood function with the suppression of oxidative stress and NLRP3 inflammasomes.[87] Furthermore, moderate MT doses (40–80 mg kg^{-1}) mediated robust anti-inflammatory activity with the modulation of the NF-kB–NLRP3–caspase-1 pathway, whereas 80 mg kg^{-1} MT activated the BDNF–ERK–CREB pathway and improved a more complex cognitive function.[87]

High doses of MT are recommended for treating the neuroinvasiveness associated with COVID-19 outbreak, as this may help regulate the immune response and neuroinflammation caused by SARS-CoV-2 (Fig. 2). MT-mediated signaling may influence reduced SARS-CoV-2 entry. When SARS-CoV-2 infects the CNS cells, it triggers the release of pro-inflammatory cytokines, for instance, (i) TNF-α, which acts by binding to TNFR receptor recruiting TRADD. This protein binds to TRAF2 to phosphorylate and activate IKK. Then, the IKK complex phosphorylates IKBα, resulting in the translocation of NF-κB to the nucleus, where it targets many genes coding for mediators of inflammatory responses. (ii) IL-6 induces gene activation in response to cytokine receptor stimulation. STAT3 proteins dimerize and translocate to the nucleus. JAK2/STAT3 signaling acts as a pivotal mediator of neuroinflammation. (iii) The binding of SARS-CoV-2 protein to the TLR (TLR3/7/9) upregulates the pro-inflammatory transcription factor NF-κB and causes the release of pro-IL-1β which is cleaved by caspase-1, followed by NLRP3 inflammasome activation. Interestingly, MT may revert these pro-inflammatory effects by inhibiting JAK2/STAT3 signaling pathway and NF-κB translocation.[88] MT is also considered to be a particularly well-suited drug to

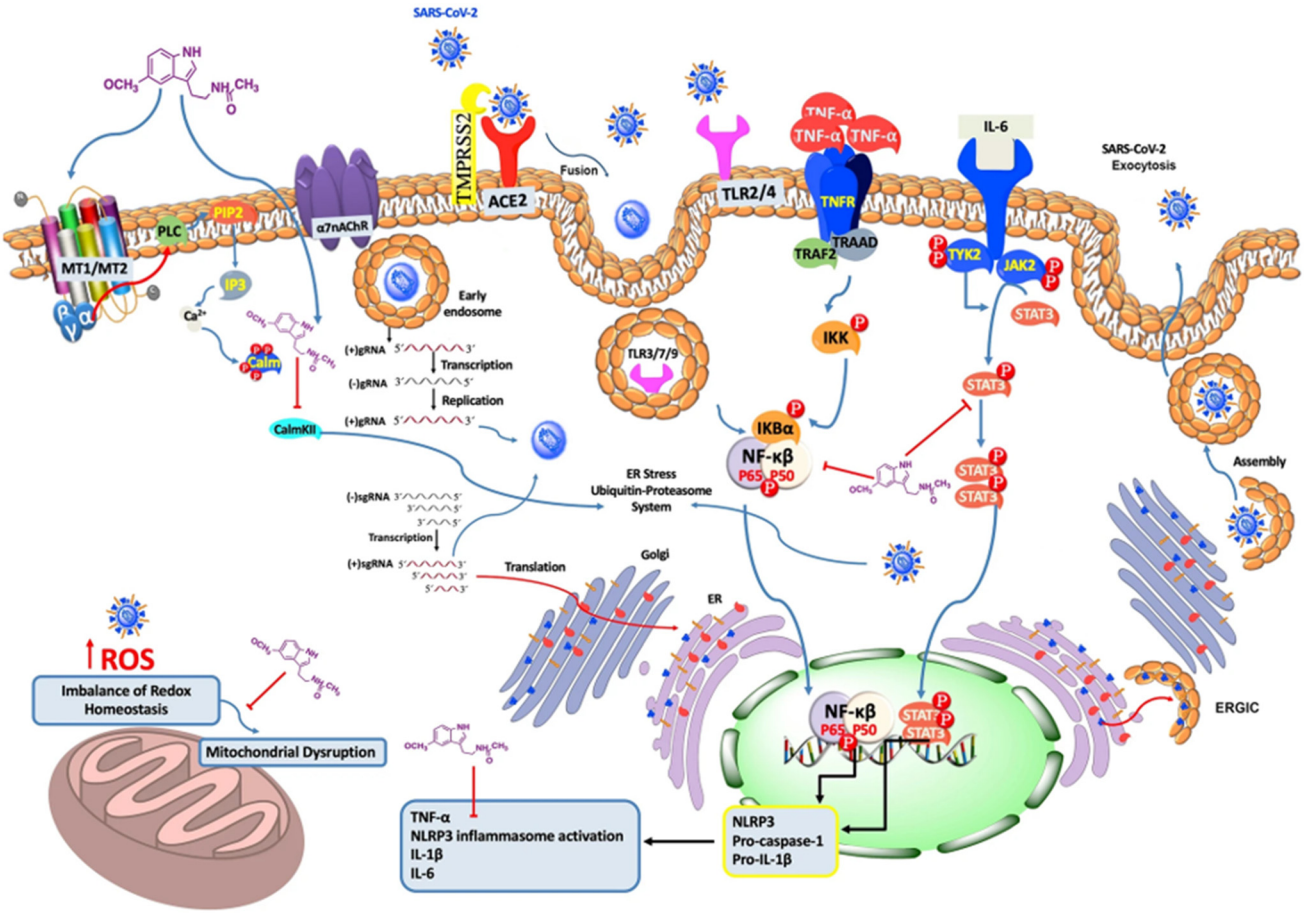

Fig. 2 Hypothetical diagram of potential therapeutic targets where melatonin may act against SARS-CoV-2 infection in the central nervous system (CNS). The virus enters neuronal cells *via* ACE2 and TMPRSS2, triggering clathrin-mediated endocytosis, and replicates inside the cell. This replication involves the synthesis of viral RNA and proteins, which are assembled in the ER and Golgi, forming new virions that are released by exocytosis. SARS-CoV-2 infection may disrupt mitochondrial metabolism, increase ROS, and induce ER stress. MT, with its high diffusibility, enters neuronal cells, binds to CaM, and may regulate the Ca^{2+}/CaMKII system, modulate ACE2 expression, link ER stress to the inflammatory response, and scavenge ROS. MT-mediated signaling may influence viral entry through either MT1/MT2 and α7nAChR receptors. The virus triggers the release of pro-inflammatory cytokines like TNF-α and IL-6, and activates TLRs, leading to inflammation through pathways such as NF-κB and JAK2/STAT3. MT may counteract these effects by inhibiting these pathways and reducing inflammation (including the inhibition of NLRP3 inflammasome activation). The diagram shows stimulation (in blue) or inhibition (in red) of therapeutic targets by MT or SARS-CoV-2 protein. Organelles and structures are not drawn to scale[88] (reproduced from ref. 88 under PMC Open Access License. Copyright © 2020, Springer Nature).

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modulate acute and chronic inflammatory activity around neural electrode implants, translating into a more stable and reliable interface.[89]

2.2.5 Autophagy, apoptosis, and DNA damage repair. Autophagy and apoptosis are the key self-destructive processes that maintain cellular balance and are regulated by signal transduction. Stress conditions (*e.g.*, calcium efflux, ER stress, and oxidative stress) activate molecules like p53 and VEGF, leading to altered gene expression and disrupted signaling pathways (*e.g.*, mTOR, Bcl-2, BH3, MAPK, JNK, PI3K/Akt, and caspases). This disruption causes protein misfolding and excessive neurotoxicity leading to neuronal death by triggering autophagy and apoptosis, with autophagy playing a dual role in either activating or inhibiting apoptosis pathways.[90] Autophagy is a fundamental cellular process that breaks down aggregated or misfolded proteins and abnormal organelles. It plays an important role in neurological damage and various neurodegenerative diseases. Abnormal regulation of neuronal autophagy results in the buildup and deposition of irregular proteins, disrupting neuron homeostasis and contributing to neurodegeneration. Autophagy plays a dual role, acting as both a protective mechanism and a pathway leading to programmed cell death. MT can exert its beneficial effects through either promoting or inhibiting autophagy, depending on the specific cellular context. MT helps regulate autophagy through LC3-II, Beclin1, P62, and mTOR pathways, and also modulates CDK5 and GSK3 to maintain the cellular balance.[91]

Oxidative stress mediates chemical damage to DNA, resulting in a wide variety of byproducts. MT and several of its metabolites can repair the sites of direct (chemical) oxidation in DNA. They can repair guanine-centered radical cations through electron transfer at extremely high, diffusion-limited rates, and also repair carbon-centered radicals in the sugar component of 2′-deoxyguanosine *via* hydrogen atom transfer. Furthermore, the MT metabolites 6-hydroxymelatonin and 4-hydroxymelatonin are also predicted to repair OH adducts in the imidazole ring.[92]

2.2.6 Neuronal cell survival and neurogenesis. The neurotrophin brain-derived neurotrophic factor (BDNF) and its high-affinity receptor, TrkB, are of considerable interest in nanomedicine development for neuronal and synaptic repair. Increased activation of the transcription factor cAMP response element-binding protein (CREB) has been shown to boost BDNF gene expression, thereby enhancing the production of endogenous BDNF.[93] MT promotes neuronal survival and neuronal regeneration through multifaceted regulation of the BDNF/TrkB/CREB signaling pathway. MT exerted anti-apoptotic and neuroprotective effects in the inner retinal neurons after hypoxia-ischemia, at least partly due to modulation of the BDNF–TrkB pathway. Elevated cleaved caspase-3 and Bax protein levels and reduced Bcl-2 protein levels in response to hypoxia-mediated ischemia diminished after MT treatment. Moreover, MT increased BDNF and downstream phospho-TrkB/Akt/ERK/CREB levels. ANA12, a TrkB receptor antagonist, antagonized these MT actions and reduced MT-induced neuroprotection.[94]

Cuprizone (a copper-chelating agent) treatment disrupts hippocampal neurogenesis in the dentate gyrus by reducing BDNF levels and decreasing CREB phosphorylation, effects that are alleviated by MT treatment.[95] Preventive MT treatment restored the propofol-induced inactivation of PKA/CREB/BDNF signaling and reversed synaptic dysfunction.[96] MT1/MT2 receptor activation by agonists increases the neuronal content of BDNF regardless of which of the two MT receptors is expressed by the neurons. On the other hand, the BDNF-stimulatory action of ramelteon (melatonin receptor agonist) appeared to involve translational rather than transcriptional mechanisms.[97] MT and its immediate precursor *N*-acetylserotonin (NAS) mediated the protective effect of ketamine-induced downregulation of BDNF protein levels as well as decreased phosphorylation of ERK and AKT. MT appears to increase BDNF levels *via* MT receptor(s) activation and stimulate TrkB, while NAS seems to activate TrkB directly.[98]

Recent studies have demonstrated that MT plays a key role in cell survival signaling pathways. Prolonged drug administration improved neuronal survival through the AKT and MAPK signaling pathways after focal brain ischemia in mice. The elevated expression of CREB and Atf-1 highlighted the significant role of MT in promoting neuronal regeneration.[99] MT treatment counteracts energy depletion and protects against brain damage through the regulation of p-AMPK/p-CREB signaling pathways in the mouse brain.[100] MicroRNA-132 is essential for neuronal survival and significantly contributes to the pathological process of AD. Treatment with MT restores the expression of miR-132 and reduces the levels of PTEN and FOXO3a. MT also prevents the nuclear translocation of FOXO3a, thereby inhibiting its pro-apoptotic pathways.[101] Thus, MT is also able to provide neuroprotection against Aβ-induced neurotoxicity through the miR-132/PTEN/AKT/FOXO3a pathway.

2.3 Clinical trials and limitations of melatonin

While preclinical studies strongly support the safety and efficacy of MT as a neuroprotective agent, clinical research remains limited. Most of the clinical trials have focused on the effects of MT on improving sleep and cognitive impairment, or on its use as an adjuvant therapeutic molecule. A meta-analysis has underscored the potential importance of MT in treating specific primary sleep disorders. MT needs to be prescribed early and used long-term at a dose of 2 to 5 or 10 mg.[102] MT supplementation (2 mg day^{-1}) improved subjective sleep quality and actigraphic sleep efficiency in traumatic brain injury patients.[103] Clinical studies have concluded that MT is effective in treating the irregular sleep/wake cycles associated with AD. A daily dose of 3–12 mg of MT at bedtime has proved to be particularly effective for managing REM (rapid eye movement) sleep behavior disorder in PD.[104] MT at doses of 10 mg day^{-1} or more for at least 12 weeks in immediate-release form has shown significant benefits in improving motor symptoms and sleep disturbances in Parkinson's disease (PD).[105] Evidence indicates that MT treatment for over 12 weeks may improve cognitive functioning in mild AD.[106]

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MT (3 mg) administration resulted in clinical improvement in patients with ischemic stroke.[107] Combined delivery of MT (3 mg day^{-1}) with valproate for adults with generalized epilepsy and generalized onset motor seizures has led to significantly improved clinical outcomes.[108] Another study has reported that prolonged MT release at a 4 mg dose did not reduce REM sleep behavior disorder in PD.

In the context of the COVID-19 pandemic, clinical research on MT for the symptomatic treatment or adjuvant treatment of SARS-CoV-2 viral infection has become a hot topic. Several clinical trials have tested the efficacy of MT in coronavirus inhibition, providing an understanding of the appropriate doses and effectiveness of MT against the virus.[109,110] In a randomized, double-blind, placebo-controlled trial, patients received either 3 mg of MT three times daily (n = 42) or a placebo (n = 39) for 2 weeks. MT significantly increased oxygen saturation, reduced respiratory rate, and lowered inflammatory markers such as CRP, ESR, LDH, CPK, ferritin, and D-dimer, most of which are prognostic for COVID-19. Importantly, no adverse side effects were observed. These findings suggested that MT is an effective and safe adjunctive therapy for mild to moderate COVID-19 infection.[111] Another clinical trial demonstrated that combining the oral administration of MT tablets (3 mg, three times daily) with standard treatment could significantly enhance sleep quality and blood oxygen saturation in hospitalized COVID-19 patients.[112]

The positive effects of MT on the nervous system have been demonstrated in cellular and animal models of various diseases (Table 1). Most of these studies used supraphysiological concentrations of MT and the required doses were significantly higher than those used for sleep regulation. In principle, the established role of MT in rhythmic function is not necessarily incompatible with the use of high doses to achieve 'protective' effects.[113] However, one needs to carefully distinguish the effects of endogenous MT from the effects observed with high doses of exogenous MT.[114] MT is available as a supplement in several Western countries (including the United States and Western Europe) in doses ranging from 1 to 10 mg. Limited clinical trials have demonstrated the potential application of MT in AD and PD, especially in the early stages of the disease. Calculations derived from animal studies suggest that cytoprotective MT doses are in the range of 40–100 mg day^{-1}. Clinical trials have reported doses as high as 100 mg, which is regarded as a substantial dosage—the highest level documented so far.[115] Evidently, there is an urgent need for clinical studies and safety assessments within this dosage range.[104,116] Although MT is considered a non-toxic natural molecule, the safety of its long-term use, especially for the additional risks that may arise from the elderly and young children, requires more intensive clinical research[117,118]

It is worth mentioning that MT has low water solubility, short half-life, and poor bioavailability. In healthy volunteers, the elimination half-lives of oral administration or intravenous administration of 10 mg of MT were 54 minutes and 39 minutes, respectively. Although there were significant individual differences, the median absolute bioavailability of oral MT was as low as ~2.5% (1.7–4.7%).[119] An early study found that even with higher oral doses of MT (100 mg), the peak concentration in human plasma was only 0.435 μM after 60 min.[120] However, MT was typically administered at dosages greater than 1 μM in preclinical investigations, and a dose of 1 mM served as the foundation for most trials. Thus, it is unlikely that either humans or animals would naturally attain such concentrations, and certainly not over an extended period of time.[114]

In recent strategies, the undesirable poor bioavailability of small molecule drugs such as MT in clinical applications could be overcome by introducing nanoencapsulation and delivery technologies. These strategies aim to construct nanocarrier systems with the potential for targeting and controlled release of drugs. Since the Food and Drug Administration approval of Doxil (a stealth liposome encapsulating doxorubicin) in 1995, more than 50 nanopharmaceuticals have entered clinical practice, with many more under investigation for various therapeutic indications.[121,122] Diverse nanoformulations, including liposomes (LP), polymers, nanocrystals, inorganic nanoparticles, micelles, and protein-based carriers, have been explored primarily for cancer therapy, oncology, fungal infections, and pain management, with lipid-based nanoparticles leading the field.[121] However, the safety and efficacy of nanopharmaceuticals, along with the lack of specific regulatory guidelines and cost–benefit considerations, remain key concerns.[122,123]

Several MT nanomedicines have been studied at the cellular and animal levels. However, a significant limitation remains the lack of pharmacokinetic and pharmacodynamics data on MT nanocarriers in animal models (in both blood and brain),[124] particularly in neurodegenerative and neurological disorders. A recent study used a microdialysis system to measure real-time melatonin (MT) concentrations in the brains of freely moving animals.[125] Each animal received an equivalent MT dose (10 mg kg^{-1}) from three different formulations. MT-loaded LP and nanoemulsions (NE) demonstrated superior pharmacokinetic parameters—longer half-life ($T_{1/2}$), higher maximum plasma concentration (C_{max}), shorter time to peak concentration (T_{max}), and greater overall drug exposure (AUC)—compared with MT dissolved in DMSO.[125] These findings provide crucial insights for preclinical research and could facilitate the clinical translation of MT-based nanocarrier formulations.

3 Nanocarrier-mediated melatonin delivery

Many nanoparticles (NPs) can encapsulate either lipophilic or hydrophilic drugs, genes, proteins, and peptides, protecting them from degradation, improving drug stability, prolonging plasma half-life, reducing side effects, and controlling the release of active components at the desired site.[126]

Liposomes (LP), solid lipid nanoparticles (SLNs), and nanostructured lipid carriers (NLCs) have been extensively studied as lipid-based nanocarriers for brain disease treatment over the past 30 years. The lipid composition provides superior bio-

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compatibility and safety compared with polymeric and inorganic nanoparticles, allowing them to cross the BBB without requiring additional functionalization.[128] Polymeric nanoparticles offer tunable size, shape, physicochemical properties, and surface modifications, enabling controlled and sustained drug delivery across the BBB. However, their degradation can generate acidic by-products, leading to potential toxicity that limits long-term brain applications.[128] Inorganic nanoparticles, while highly stable and chemically versatile, also pose inherent toxicity concerns. Despite their advantages, lipid-based nanoparticles face challenges such as oxidation and drug leakage, which hinder their clinical translation. Complex hybrid systems (multi-lipid, lipid-polymer, *etc.*) offer a promising solution, balancing stability, safety, and efficacy for brain-targeted drug delivery. For example, ionizable lipids have been designed to form strong ionic interactions with encapsulated drugs, while cholesterol enhances the structural integrity to ensure tighter drug packing. Additionally, modifying the particle surface with polyethylene glycol prolongs circulation time.[121]

Fig. 3 summarizes a variety of nanocarriers for MT encapsulation and delivery including lipid-based nanocarriers, polymer-based nanocarriers, hybrid lipid–polymer nanocarriers, inorganic NPs, and mesoporous nonlamellar liquid crystalline lipid NPs (cubosomes). MT-loaded NPs have received attention due to beneficial features such as (i) improving drug bioavailability by increasing water-solubility and prolonging the duration of MT action; (ii) providing a biphasic release profile (an early burst release phase followed by a slow release phase), (iii) environmentally sensitive (pH- or temperature-) responsive release; or (iv) targeted delivery of MT facilitated by ligands or peptides anchored on the NP surface.

3.1 Lipid-based nanocarrier-mediated melatonin delivery

The lipid-based nanocarrier systems for drug delivery mainly include vesicle-type systems like LP, ethosomes (ET), transfersomes (TF) and niosomes (NS), NE systems, and particulate systems such as SLNs and NLCs.[129] Table 2 summarizes the lipid-based nanocarrier systems investigated for efficient MT delivery. These carriers are typically made of naturally occurring lipids that are well-tolerated by the human body. Incorporating water-insoluble drugs into such formulations enhances their solubility and stability in aqueous environments, removing the need for harmful co-solvents or pH adjustments to dissolve hydrophobic drugs.[130] These NPs confer safety for therapeutic use and limit the drug degradation phenomena.[131]

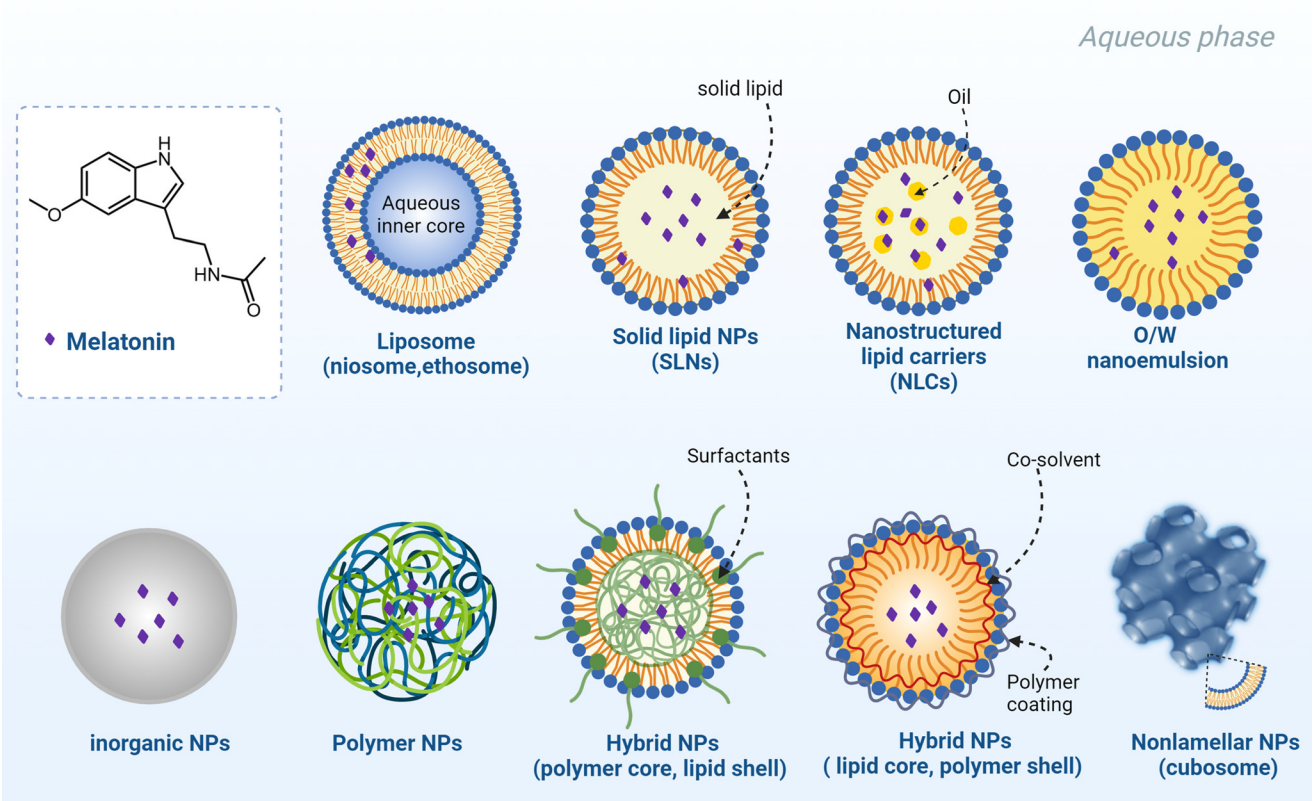

Fig. 3 Chemical structure of MT (*N*-acetyl-5-methoxyindolamine) and a schematic presentation of different types of nanocarrier suitable for the encapsulation and protection of MT as a drug. MT was initially discovered in 1958 by Lerner who isolated it from the extract of bovine pineal tissue.[127] MT is a derivative of tryptophan, an essential amino acid for mammals, which contains a indole heterocycle and two side chains, namely, a 5-methoxy group and 3-amide group.[51] Promising nanocarriers of MT include lipid-based nanocarriers like liposomes, solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), and nanoemulsions, inorganic NPs, polymer NPs, lipid–polymer hybrid nanoparticles, and non-lamellar liquid crystalline lipid NPs (*e.g.*, cubosomes) (created with *BioRender*).

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Table 2 Lipid nanocarrier-mediated melatonin delivery

Type	Formulation	Studied model	ROA	EE%	LE%	Release profile	Outcome
LP, NE	LP: DSPC/cholesterol/ PEG2000-DSPE NE: tricaproin, soybean oil, medium-chain triglycerides (MCT)	*In vivo* brain microdialysis: female Sprague–Dawley rats aged 12 weeks	25 mg kg^{-1} (i.v.)	N.A.	N.A.	Prolonged release, $T_{1/2}$: 81, 50, 26 min for MT-LP, MT-NE, and MT-EtOH	Lipidic NPs provide higher levels of MT in the brain, a longer time above critical pharmacological concentrations, and a similar MT concentration in the circulation compared with MT dissolved in DMSO.[125]
EL-LP	PC, cholesterol, sodium deoxycholate	Permeation: isolated dermis of mouse *In vivo*: photoaging mouse model	TD	73.9	9.92	Cumulative penetration of EL 1.5 times higher than that of conventional LP	EL more easily penetrate into the body; MT-EL enhanced the skin hydration level and preserved the integrity of dermal collagen and elastic fibers.[111]
ET-LP	Soya PC, ethanol	Skin irritancy: male albino rabbits	TD	70.7	N.A.	N.A.	MT-loaded ETs provided an enhanced transdermal flux, lower lag time, higher entrapment efficiency and low skin irritancy potential.[133]
TF NS	Cholesterol PC Tween 80 PEG 400	HFF-1 cells RAW 264.7 cells	TD	TF 74.9 NS 66.8	N.A.	Higuchi model; delayed and sustained release (TF/NS 74.8/66.8% at 24 h) *vs.* MT solution rapid release (102.3% at 8 h)	MT-loaded TF showed greater permeability, MT deposition, higher NO inhibition and stimulation of collagen than NS and MT solution.[134]
SLN	Compritol 888, Span80, Tween80	*In vivo*: male Wistar rats with testicular trauma	25 mg kg^{-1} (i.p.)	20	5	Burst release at the first 30 min followed by a sustained release pattern	Testicular trauma disturbed spermatogenesis, morphometric, and oxidative parameters. MT and especially MT-SLN improved traumatic damage.[135]
SLN	N.A.	*In vivo*: male Wistar rats with cyclosporine A (CsA)-induced cardiac damage	1 mg kg^{-1} (i.p.)	N.A.	N.A.	N.A.	(i) MT significantly reduces CsA cardiotoxicity acting also on apoptotic processes, and (ii) the reduction in CsA-induced cardiotoxicity is mediated mainly by its antioxidant effect.[136]
NLC	Caprylic/capric, triglycerides (CCT), octyl, Compritol 888 ATO, glyceryldistearate, polaxamer 407	Breast cancer MCF-7 cells	N.A.	84.3	18.7	N.A.	Co-treatment of the cells with MT-NLC and tamoxifen caused a 2-fold increase in the percentage of apoptosis; MT-NLCs on activation of apoptosis are associated with alterations in the cell cycle progression by triggering sub-G1 arrest; MT induces marked increase in Bid and Bax mRNA expression level.[137]

Nanocarrier types: liposome (LP), solid lipid nanoparticle (SLN), nanostructured lipid carrier (NLC), transfersomes (TF), niosomes (NS), ethosomes (ET), ethanolic liposome (ET-LP), nanoemulsion (NE); phosphatidyl choline (PC); route of administration (ROA): intraperitoneal injection (i.p.), transdermal administration (TD), intravenous injection (i.v.); not available (N.A.).

LP are spherical lipid bilayer structures with an aqueous core, where the aqueous volume is enclosed by one or more lipid bilayers. The bilayer typically consists of phospholipids. Based on their structure, number of bilayers, and size, LP can be categorized as small unilamellar vesicles (25–50 nm), large unilamellar vesicles (100 nm–1 μm), multilamellar (0.1–15 μm), and multivesicular (1.6–10.5 μm) particles.[132]

NE is a thermodynamically unstable colloidal mixture of two immiscible liquids, where one liquid acts as the dispersed phase and the other as the dispersing medium. NE usually consists of fine oil droplets dispersed in water, with droplet sizes typically between 100 and 600 nm.[138]

Medium-chain triglyceride NE (MCT-NE) has gained popularity as a carrier in recent years because of its unique properties, such as its capacity for enhanced solubilization of insoluble drugs, slow release rates, and increased transdermal absorption.[139] LP and NE are excellent solubilizers for lipophilic substances like MT. It has been demonstrated that intrave-

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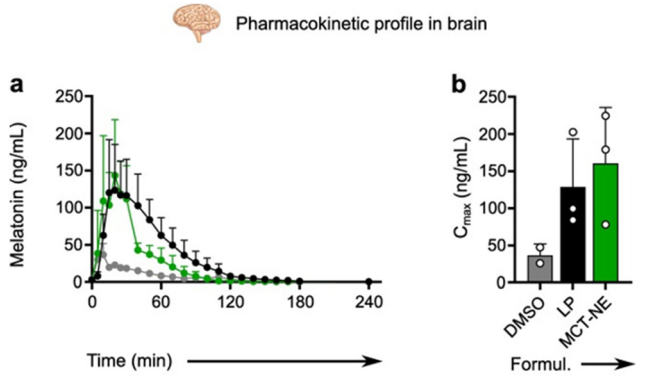

Fig. 4 Example of pharmacokinetic profiles and *in vivo* brain characterization data. (a) Melatonin concentration in the brain (mean ± SD) after a bolus injection of 10 mg kg^{-1} MT in DMSO, liposomes (LP), or medium-chain triglycerides nanoemulsion (MCT-NE). (b) Estimated pharmacokinetic parameters of MT in DMSO, LP or MCT-NE (mean ± SD); (b) maximal plasma concentration of drug (C_{max})[125] (reproduced with permission from ref. 125. Copyright © 2020, Elsevier).

nous administration of MT-nanoformulations (LP or MCT-NE) improves the drug bioavailability in the brain compared with the administration of MT dissolved in organic solvents like DMSO. Interestingly, MT pharmacokinetics in the brain is influenced by the type of nanocarrier. Fig. 4 shows that MCT-NE yielded a higher C_{max} of MT, while LP provided higher MT levels in the brain and maintained pharmacological concentrations for a longer duration.[125] Conventional LP typically do not cross the BBB *in vivo* unless disrupted or ligand-modified. A potential mechanism underlying this enhanced brain accumulation may involve NP fusion with the endothelial luminal membrane, leading to intracellular release and facilitated brain uptake.[125]

Considering the low drug entrapment efficiency and challenging large-scale manufacturing of vesicle systems, like LP, SLNs have been investigated as advanced CNS drug delivery systems.[140] SLNs are lipid-based biocompatible nanocarriers consisting of a condensed-phase lipid matrix (triglycerides, fatty acids, or waxes) that can be organized into a crystalline nanostructure. SLNs, prepared by the probe ultrasonication method, range in size from 10 to 1000 nm in diameter.[141] MT-loaded SLNs showed burst release behavior of MT at the initial stage (the first 30 min) followed by a sustained release pattern. The burst release could be attributed to the diffusion of the drug located on the surface of the SLN. Thereafter, the drug is released from the core of the SLNs, where MT is suggested to be homogeneously distributed within the NPs.[135]

NLCs have been developed as a modified version of SLNs. NLCs feature a combination of solid-phase and liquid-phase lipids, resulting in a different internal core structure compared with SLNs, which have only a solid lipid core. This structural difference introduces imperfections in the core, leading to a more performant formulation.[142] For instance, NLCs showed much higher MT entrapment efficiency (EE) (84.3 *versus* 20%) and loading efficiency (LE) (18.7 *versus* 5%) than the SLNs.[135,137]

3.2 Polymer-based nanocarrier-mediated MT delivery

Polymeric NPs, providing numerous functions such as targeting, pH response, and control release, have been extensively investigated as drug delivery systems. They range in size from 1 to 1000 nm and can encapsulate active compounds either within the polymeric core or adsorbed on the surface.[143] By utilizing polymer nanomaterials and drug-loading nanoparticle technology, MT has been either encapsulated or attached to the NPs, thereby altering the dissolution rate and enhancing drug absorption *in vivo*. The designed MT formulations improved its therapeutic efficacy against multiple diseases (Table 3).

Several natural (chitosan, hyaluronic acid, or sericin) and synthetic (PLGA, PLA, or PCL) polymers have been used as delivery systems for MT to treat a variety of pathophysiological processes.[144,145] The pH dependence of MT release was linked to the pH sensitivity of the NPs' supramolecular structure as determined by their chemical nature, for instance, the amine groups of the chitosan chains, which have a pK_a value of 6.5. In an acidic medium, these amine groups become protonated, increasing the electrostatic repulsive forces between the cationic moieties. The repulsive forces then promote the release and diffusion of MT from the nanocarriers to the acidic environment.[146]

Cyclodextrin (CD)-based molecularly imprinted nanosponges (MIP-NSs) have been used to overcome the limitations associated with MT release.[147] Gelatin, polylactic acid (PLA), and chitosan were utilized to formulate MT-loaded nanoparticles (MTNPs), which demonstrated varied controlled release profiles in different pH environments.[148] The type II collagen-targeting peptide was attached to the surface of PLGA NPs to create a nano-delivery system for MT. *In vivo*, this system remained stable for at least 21 days and persisted in the joint cavities of mice, releasing MT for at least 14 days. As a result, the injection frequency of this nano-delivery system was reduced by 75% compared with injections of MT alone.[149]

3.3 Hybrid nanocarrier-mediated melatonin delivery

Lipid and polymeric NPs are the most studied NPs and have been shown to be the most efficient drug delivery systems. Depending on the composition, some of them display instability, rapid drug release, limited drug loading capacity, low biocompatibility, and problems for large-scale production. To overcome these limitations, lipid–polymer hybrid nanoparticles (LPHNPs) have been developed to converge the advantages of lipid- and polymer-based nanocarriers in terms of biocompatibility and stability, improved drug loading and control release, providing an increased drug half-life and therapeutic effects.[150]

Hybrid NPs (LPHNPs) have been classified into two main groups based on the different arrangements of lipids and polymers, *e.g.* a polymer core with a lipid shell or a lipid core with a polymer shell. LPHNPs comprising a polymer core and a lipid shell are the simplest forms of LPHNPs. These carriers consist of three different ingredients, as shown in Fig. 3: (i)

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Table 3 Polymer nanocarrier-mediated melatonin delivery

Nanocarriers type	Formulation	Studied model	ROA	EE%	DE%	Release profile	Outcome
MT@PLGA-COLBP NPs	PLGA, DSPC, DSPE-PEG2000, type II collagen-binding peptide WYRGRL (COLBP)	Osteoarthritis model; cells: chondrocytes; *in vivo*: female C57BL/6 mice	MT 10 μL, 50 mM; NPs10 μL, 2 mg mL^{-1} injection into the knee joint	N.A.	N.A.	Continuous release during 14 days	MT protects chondrocytes by inhibiting TLR2/4-MyD88-NFκB signal pathway; NPs targeting cartilage and sustained release of MT in the articular cavity.[149]
Fucoidan/chitosan layered PLGA NPs (MNPs@C@F)	PLGA, polyvinyl alcohol (PVA), chitosan, fucoidan	Breast cancer mouse 4T1 cells; *in vivo*: BALB/c mice were orthotopically inoculated with 4T1 cells	Oral	15.1	4.1	Overcome the barriers of the GI tract and reach an effective cumulative dose at the tumor site (pH5)	MNPs@C@F promoted intestinal microfold cell transcytosis for the delivery of MT and fucoidan into tumors; MT and fucoidan in the tumors could regulate the tumor microenvironment by decreasing P-gp, Twist, HIF-1α, and anti-inflammatory immune cell expression while increasing cytotoxic T cell populations following doxorubicin treatment.[151]
Polydopamine NPs (MPDANPs)	Dopamine, cyclohexane, Tween20, ammonium hydroxide	*In vitro*: high glucose (HG)-induced DR model in ARPE-19 cells; *in vivo*: male SD rats with DR	MT 10 mg kg^{-1}; MPDANPs 20 mg kg^{-1} (i.p.)	94.6	50	Higher release at pH 6.7; controlled and extended drug release until 160 h	MPDANPs have demonstrated a reduction in VEGF- and PKCδ- levels, and ROS-mediated DR pathogenesis.[152]
Chitosan NPs	Sodium tripolyphosphate (TPP), chitosan	Cells: RAW 264.7; *in vivo*: female Balb/C mice with bowel disease	(i.v.)	N.A.	20.4	Initial burst release followed by prolonged release; cumulative release at 24 h: 76.35% at pH7.4 and 96.22% at pH4.5	Significant anti-inflammatory activity of MT-CS NPs is attributed to nitric oxide (NO) reduction, inhibited nuclear translocation of NF-kB p65 and reduced IL-1β and IL-6 expression. 2021[153]
Chitosan-TPP NPs	Chitosan (CTS), TPP	Etoposide-induced genotoxicity; cells: HepG2	N.A.	75	N.A.	A biphasic release: an early burst release phase and a slow-release phase	MT reduced the effects of etoposide significantly through the reduction of the level of DNA damage. MT decreased the intracellular ROS generation but increased the intracellular GSH levels in HepG2 cells. MT-loaded NPs were more effective than the free MT drug.
Chitosan/HPMC NPs	Chitosan, TPP, hydroxypropyl methylcellulose (HPMC)	Breast cancer; cells: MDA-MB-231	N.A.	N.A.	N.A.	Cumulative release of MT at pH 5.5 was 61%, while it was 18% at pH 7.5.	The toxicity of MT encapsulated in CTS/HPMC NPs was found to be higher than that of the free MLT, indicating that MT encapsulation facilitated its uptake in the cancer cells.[146]
Gelatin-PLA-CTS NPs	PLA, gelatin, chitosan, Span-80, Tween-80	*In vivo*: pinealectomized male Wistar rats	MT, 10 mg kg^{-1}; NPs, 60 mg kg^{-1} (s.c.)	33.82	15.77	Controlled-release; pH-sensitivity	Drug release from MT-loaded NPs was more sensitive in simulated intestinal fluid (pH 7.4) and blood (pH 6.8) and displayed better antidepressant actions compared with the free MT.[148]
Sericin-based NPs (MR-SNC)	Sericin, resveratrol	Breast cancer; cells: MCF-7	N.A.	98	27	An apparent burst release (67%) of MT occurred in pH 6 at 55 h.	The efficient cellular uptake of MR-SNC, DNA fragmentation and chromatin condensation was found at pH 6. Proficient release of the entrapped drugs occurred from MR-SNC in an acidic environment leading to cell apoptosis.[145]

COLBP: Type II collagen-binding peptide; CTS: chitosan; HPMC: hydroxypropyl methylcellulose; TPP: tripolyphosphate; route of administration (ROA): intravenous injection (i.v.); intraperitoneal injection (i.p.); not available (N.A.).

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the inner polymer core that encapsulates the active therapeutic compounds; (ii) the lipid monolayer that encapsulates the polymer core; and (iii) the external lipid–PEG layer, whose role is to stabilize and prolong the systemic circulation (*i.e.*, to ensure that nanoparticles stay in the body for a long time).[154] The natural or synthetic biomimetic lipids and the biodegradable polymer core together constitute an advanced and beneficial delivery system that can be used to treat a variety of diseases through systemic or local drug delivery.[155]

Typically, lipid-core/polymer-shell systems include a lipid core and one or more polymer surface layers. The core encapsulates the active ingredient, while the surface coating improves the NP stability and interaction with biological barriers. Several studies have functionalized lipid nanocarriers (SLNs, NLCs, or LP) with polymer shells (chitosan, PEG) to fabricate chitosan-coated lipid NPs, PEGylated lipid NPs, or multilamellar objects.[156] Chitosan-coated LP were used as carriers of MT, with an encapsulation efficiency between 34.4% and 60.8%. The presence of chitosan on the LP surface led to a decrease in the thickness of the lipid bilayer, suggesting that the biopolymer modifies the lipid nanostructure or its hydration.[157]

Table 4 summarizes the hybrid types of LPHNP used as MT carriers with controlled and sustained release characteristics.[158,159] Previous research with chosen experimental models has focused on evaluating the antioxidant effects[160] and the anti-apoptotic properties[161] of MT-encapsulated NPs.[162] As an example, the conjugated yne-ene chain of the polymeric backbone of polydiacetylene has enabled the formation of stable nanoaggregates from which only 50% of the encapsulated MT has been released after 72 h under physiological conditions.[159] A 2-hydroxypropyl-β-cyclodextrin (HPβCD) grafted solid lipid nanoparticle (SLN)-based bioconjugate has been synthesized and used for administering a combination of MT and amphotericin B (AmB) orally for effective visceral Leishmaniasis treatment. The formulations (HPCDMT-AmB SLN) showed a high loading capacity and a high entrapment efficiency of AmB (%DL = 9.0 ± 0.6 and %EE = 87.9 ± 0.6) and MT (%DL = 7.5 ± 0.5 and % EE = 63 ± 6.2). The cumulative percent release of AmB and MT was 66.1% and 73.1%, respectively, up to 72 h.[158]

A nanoscale system, consisting of ethylcellulose, medium chain triglyceride (MCT), and surfactants (Span60 and Tween80), has been developed for the controlled topical administration of MT in the retina. It enabled an enhanced neuroprotective effect of MT on the retinal ganglion.[161] MT-loaded lipid-core nanocapsules (MT-LNCs) upregulated mRNA levels of catalase (CAT) and superoxide dismutase 2 (SOD2) genes (Fig. 5), while down-regulating the transcription levels of the pro-apoptotic BCL2-associated X protein (BAX), cysteine peptidase 3 (CASP3), and SHC-transforming protein 1 (SHC1) genes.[160] Such effects have not been substantial enough for polymer carriers (MT-NC) alone.

3.4 Other types of nanocarrier for melatonin delivery

Other types of nanocarrier, including silica NPs,[163] nanofibers,[164] metallic or non-metallic NPs,[165] protein nanodots,[166] graphene-dendrimeric systems,[167] and cell-derived exosomes,[168] have been engineered to overcome MT's challenges such as poor solubility, stability, and bioavailability, and enabling sustained delivery in certain systems. Magnetite–silica–carbon quantum dot nanocomposites were synthesized for MT controlled-release as an anticancer drug.[163] Yadav *et al.* evaluated the biological efficacy of MT-loaded protein nanodots for live-cell imaging and enhanced nano-drug delivery efficacy in a breast cancer cell line.[166] MT-selenium NPs showed hepatic protective activity associated with antioxidant properties such as inhibiting lipid peroxidation and NO production as well as increasing antioxidant enzyme action.[165] A functionalized graphene-dendrimeric system was designed by using Fe_3O_4 NP as a magnetic nanocarrier for co-delivery of doxorubicin and MT.[167] Engineered M2 macrophage-derived exosomes (M2-exos) were used for MT loading and effective treatment of periodontitis thanks to the fact that M2-exos can target inflammatory sites and modulate immune microenvironments. MT-loaded M2-exos have positively affected inflammatory bone loss in periodontitis by mediating ER stress and immune reprogramming.[168] Moreover, studies have shown increased cytotoxicity and apoptosis when MT was used in combination with some metal NPs such as ZnO[170] and Pd NPs.[171] This effect helped achieving anti-cancer cell proliferation outcome.

4 Perspectives for development of melatonin-based nanomedicines for the nervous system

Despite the fact that MT is thought to cross the BBB, nanomedicines aiming at the improvement of MT therapeutic efficacy face big challenges. Nanomaterial-based BBB-crossing strategies have been broadly used for the brain delivery of theranostic agents, including intranasal delivery, temporary disruption of the BBB, local delivery, cell-penetrating peptide (CPP)-mediated BBB crossing, receptor-mediated BBB-crossing, shuttle peptide mediated BBB-crossing, and cell-mediated BBB crossing.[172]

4.1 Nose-to-brain delivery of nanomedicines

Nose-to-brain delivery has been explored as a non-invasive method that bypasses the BBB, allowing direct access to the brain *via* the olfactory and trigeminal nerves (Fig. 6A).[173,174] The five major pathways through which drugs are transported across the BBB are summarized in Fig. 6B. Particularly, lipid-based and polymer-based carriers are beneficial for CNS delivery due to their safety, high drug-loading capacity, and controlled-release features.[174] The intranasal route of nanocarrier administration, *e.g.* NLCs, SLNs, or NE, appeared to be advantageous for targeted drug delivery to the brain. Such NPs were employed for MT loading and demonstrated the ability to cross the BBB.[175] MT-loaded vehicles for intranasal delivery have been studied *in vitro* and in animal models representing

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Table 4 Hybrid nanocarrier-mediated melatonin delivery

Nanocarriers	Formulation	Studied model	ROA	EE%	DE%	Release profile	Outcome
HPCD-MT-AmB SLN	2-Hydroxy 3-propyl beta-cyclodextrin, glyceryl monostearate, PVA, AmB	Visceral Leishmaniasis cells: *L. donovani*-infected J774A.1 macrophages, *in vivo*: BALB/c mice and Swiss albino mice	Oral 10–20 mg kg^{-1}	AmB ~87.9; MT ~63	AmB ~9.0; MT ~7.5	Burst release and then slow sustained diffusion until 72 h, AmB 66.1%; MT 73.1%	Efficiency of MT in combination with amphotericin B, delivered by HPβCD-modified SLN, to inhibit the infection.[158]
Polymer-coated lipid-core nanocapsules (LNCs)	CCT, sorbitan monostearate, PCL, Tween 80	*In vivo*: paraquat (PQ) intoxicated *Caenorhabditis elegans*	Oral 0.96 mg mL^{-1}	39	N.A.	N.A.	Pretreatment with MT-LNC increased the survival rate, reduced the ROS, and maintained the development in *C. elegans* exposed to PQ; demonstrated uptake and distribution of MT-LNC in a nematode; while LNC was not toxic, MT-LNC prevented the effects of PQ poisoning.[169]
Ethylcellulose NPs (NCECMEs)	Ethylcellulose, Span 60, MCT	Retinal degeneration; *in vivo*: white female rabbits	Topical in eyes 50 μL per /2 h; 8 h per day for 9 days	67–73	N.A.	Drug release fitted by a Korsmeyer–Peppas model	Greater permeation capacity of MT observed in NCECMEs providing higher neuroprotective and antiapoptotic effects on RGCs.[161]
Polymeric (NC) and lipid-core nanocapsules (LNC)	CCT, PCL, Tween 80, Span 60	*In vitro* cultured bovine embryos	N.A.	N.A.	N.A.	N.A.	MT-LNC increased embryo cell number at the concentration (10^{-9} M), decreased cell apoptosis and ROS levels, down-regulated mRNA levels of BAX, CASP3, and SHC1 genes, and upregulated mRNA levels of CAT and SOD2 genes.[160]
Polymer/lipid hybrid nanovesicles (Lip-MT)	PCDA; DMPC	Bone formation; *in vivo*: zebrafish; cells: C3H10T1/2, mouse mesenchymal stem cells	N.A.	47.26%.	N.A.	A steady increase over time up to 108 h	The Lip-MT elevated the expression of key transcription factors (Runx2, type 1 col mRNAs) and the secretion of extracellular matrix proteins that are related to osteoblast differentiation. The bone formation in a zebrafish model was enhanced after exposure to Lip-MT compared with MT.[159]

Not available (N.A.).

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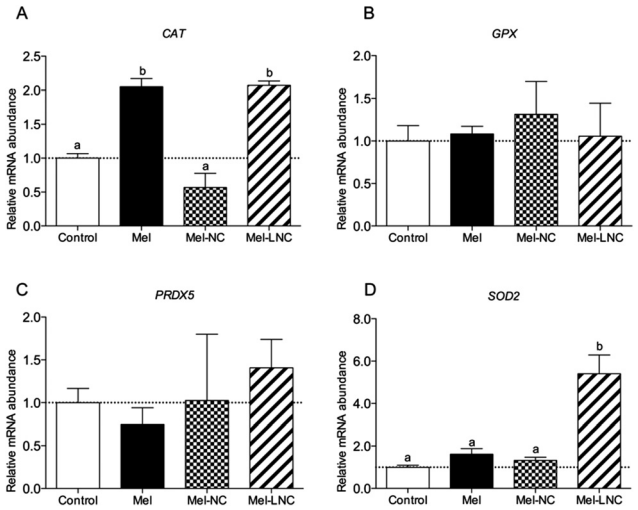

Fig. 5 Effects of free and nanoencapsulated melatonin (10^{-9} M) on the relative mRNA abundance of oxidative stress-related genes.[160] (A) catalase (CAT) gene; (B) glutathione peroxidase (GPX) gene; (C) peroxiredoxin (PRDX5) gene, and (D) superoxide dismutase 2 (SOD2) gene. The small symbols a and b above the histograms indicate significant differences between groups ($P < 0.05$). Mel = non-encapsulated MT, Mel-NC = melatonin-loaded polymeric nanocapsules, Mel-LNC = melatonin-loaded lipid-core nanocapsules (reproduced from ref. 160 UNDER open science license. Copyright © 2016, PLOS Open Access Publisher).

conditions such as ischemic stroke,[176] cerebral ischemia[177] and glioblastoma[178] (Table 5). The intranasal drug delivery systems have proved to be more effective for CNS delivery as compared with other routes or suspensions of non-encapsulated drugs.[179] It has been reported that MT-loaded lipidic nanocapsules (MT-LNCs) have a 10.35 times higher permeation of MT than the drug solution across sheep nasal mucosa. This helped promoting neuronal survival by lowering oxidative stress and anti-inflammation.

Fig. 7 shows the effects of free MT and MT-LNC treatments on hippocampal neurons in an ischemic stroke model.[176] The sham-operated rat sections revealed intact neurons with a robust architecture in the hippocampal region (Fig. 7(A,a)). In contrast, following ischemia–reperfusion, there was evident selective and extensive damage in the hippocampal CA1 area 5 days post-ischemic insult (Fig. 7(B,b)), characterized by neurons showing shrunken cytoplasm with pyknotic nuclei (indicated by black arrows), accompanied by a decrease in the number of viable neurons. Post-ischemia administration of MT-LNCs (Fig. 7(D,d)) significantly restored the pathological changes in the hippocampal neurons. The treatment with MT-LNC was more effective as compared with MT solution (free drug) (Fig. 7(C,c)).[176]

4.2 Innovative strategies with melatonin-based nanomedicines for neurological diseases

Table 5 summarizes recent advances in the development of MT nanomedicines for treating neurological diseases. Targeted delivery, multi-drug loading, and multifunctionality are several potential and attractive strategies, which enable MT-based nanomedicines to better exert their neuroprotective and neuroregenerative effects, promoting their role in the prevention and treatment of neurological disorders.

Targeted formulations play a crucial role in enhancing efficacy by precisely directing the delivered drug to specific tissues. Many approaches can create targeted nanoformula-

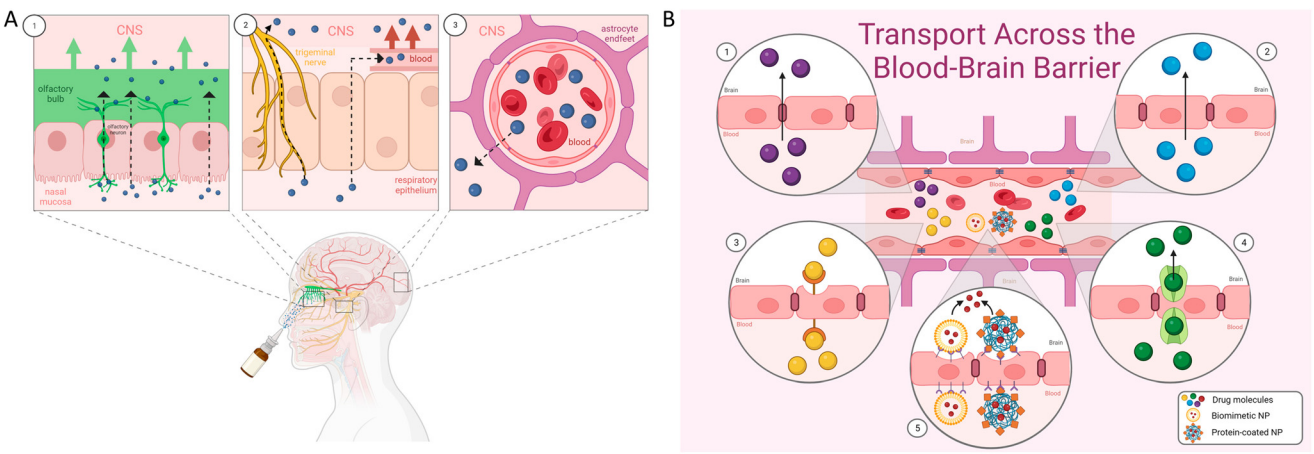

Fig. 6 (A) (1) Direct transport of intranasal drugs from the nasal mucosa to the olfactory bulb may occur by axonal transport along olfactory neurons or *para*- or transcellular transport across the nasal epithelium. (2) In the respiratory region of the nasal cavity, drugs can be endocytosed by the trigeminal nerve and travel along the axon to reach the CNS. They may also cross the epithelial cell layer to reach the blood. (3) Once in the blood, drugs administered intranasally need to cross the BBB to reach the CNS; (B) transport across the BBB primarily occurs by paracellular transport (1), passive diffusion (2), receptor-mediated transcytosis (3) or carrier-mediated transport (4). Nanoparticles (NPs) can also cross the BBB for CNS drug delivery under certain conditions (5); biomimetic NPs synthesized using physiological proteins, cell membranes or viruses take advantage of the natural uptake of these biomaterials. Additionally, synthetic nanoparticles can be coated by targeting ligands such as transferrin, P-glycoprotein, and angiopep-2 that bind to receptors located on the BBB cells to facilitate permeation of the BBB and drug release within the brain parenchyma[174] (reproduced under open access Creative Commons Attribution (CC BY) license. Copyright © 2023, MDPI).

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Table 5 Recent innovative strategies for the development of melatonin nanomedicines for neurological diseases

Nanocarrier	Disease/state	Studied model	Administration route	Outcome	Year/ref.
MT-loaded human serum albumin nanoparticles (MT@HSAnps)	PD	*In vitro* release: dialysis bag (12 kDa); cell line: SH-SY5Y cells; *in vivo*: BalB/C mice	i.p.	MT@HSAnps showed a controlled drug release profile (initial burst release and sustained release later). The neurotherapeutic efficacy of MT-loaded HSAnps in preventing rotenone-induced PD was attributed to enhancing BMI1-mediated PTEN degradation and mitophagy induction.	2024[180]
Lipidic nanocapsules (LNCs)	Ischemic stroke	*Ex vivo* permeation: sheep nasal mucosa; *in vivo* (male rats): cerebral ischemia/reperfusion (I/R)	Intranasal	LNCs exhibited 10.35-fold higher permeation of MT than free drug solution; MT-LNCs favored reduced oxidative stress with lower MDA levels, higher GSH and SOD levels, decreased inflammatory markers (TNF-α, NO, MPO), and significant inhibition of caspase-3 activity. WB analysis showed recovery of Nrf-2 and HO-1 protein expression, downregulation of key inflammatory markers (NF-κB, p65, iNOS, Bax, Cyt C), and upregulation of Bcl-2, promoting neuronal survival.	2022[176]
Polymeric nanocapsules (PNCs)	Brain ischemia	*Ex vivo* permeation: sheep nasal mucosa; *in vivo* (male rats): global cerebral ischemia/reperfusion	Intranasal	MT-PNCs displayed 8-fold higher permeation than the free drug solution; MT revived the I/R-mediated disruption of Nrf-2/HO-1 as a protective pathway; the neuroprotective/anti-apoptotic effects of MT and MT-PNCs counteracted neuronal death, decreased apoptotic markers, and increased the pro-surviving protein Bcl-2; MT-PNCs displayed better therapeutic performance as compared with MT solution alone.	2022[177]
Poly-caprolactone nanoparticles (PCL)	Glioblastoma	*In vitro* drug release: dialysis tubes (12–14 kDa); cell lines: U87MG and MRC-5 cells; *in vivo* (male rats): brain fluorescence tomography, MT quantification in brain and plasma	Intranasal and oral	MT-NP increased the drug apparent water solubility ~35 fold; MT-NPs demonstrated strong activity against U87MG cells, resulting in an IC_{50} ~2500 fold lower than that of the free drug; FMT images revealed rapid translocation and accumulation of NPs from nasal cavity to the brain. Intranasal administration of MT-NPs resulted in higher AUC brain and drug targeting index compared with the free drug by either intranasal or oral routes.	2019[178]
Melatonin niosomes (MN)	Preclinical evaluation	Cell lines: IMR-32 (neuroblastoma) and RPMI 2650 (human nasal septum carcinoma) cells; *in vivo* (male rates): evaluated acute and subchronic toxicity	Intranasal and i.v.	Intranasal MN was bioequivalent to i.v. MT providing therapeutic level doses. Acute and subchronic toxicity screening showed no abnormal signs, symptoms or hematological effects in any animals. The intranasal MN could deliver MT to the brain to induce sleep and provide delayed systemic circulation (relative to i.v.) as well as distribution to peripheral tissues.	2017[32]

tions, including custom biomolecules such as antibodies or aptamers. Recently, much attention has been paid to biomimetic nanoparticle platforms that exploit targeting specificities, like small molecules (folate and riboflavin), carbohydrates, cell-penetrating peptides, proteins (transferrin or lipoproteins) and even mammalian cell membranes naturally found in living systems. These strategies have evolved over time to maximize functionality.[181] The biomimetic targeting

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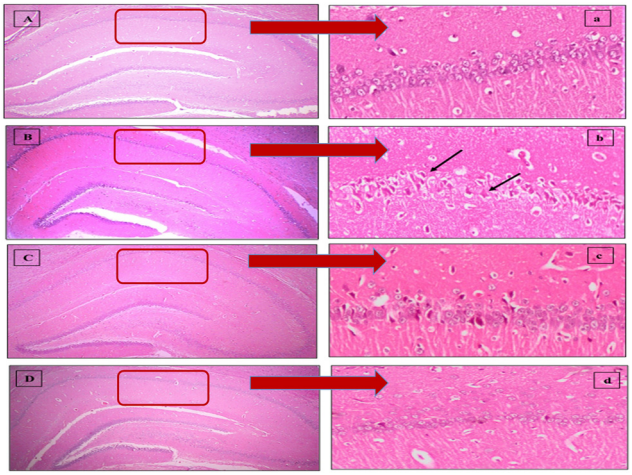

Fig. 7 Photomicrographs (×400) of hematoxylin and eosin (H&E) staining revealing the neuroprotective effect of melatonin (MT) on the hippocampal CA1 region. (A,a) Sham, (B,b) ischemia/reperfusion (I/R), (C,c) MT solution-treated group, and (D,d) MT-lipid nanocapsule (LNC)-treated group[176] (reproduced with permission from ref. 176 under PMC Open Access License. Copyright © 2022, Taylor & Francis Publisher).

nanosystems have received widespread interest in the therapeutic field of neurological diseases. The use of cell membrane-coated NPs for targeted drug delivery to the brain and treatment of neurological disorders has been recently summarized.[182]

Intracellular targeting is an effective method to improve drugs' therapeutic index by delivering the active therapeutic substance directly to its intracellular site of action. This involves targeting not just tissues or cells, but specifically the subcellular organelles such as lysosomes, mitochondria, nuclei, and Golgi/ER. It is considered as the third level of drug targeting.[183] Mitochondria-targeted biomimetic NPs have been reported to control mitochondrial dysfunction in neurons and improve PD treatment. These Cu2-xSe-based NPs, functionalized with curcumin and enveloped in a DSPE-PEG2000-TPP-modified macrophage membrane, were able to efficiently target the mitochondria of damaged neurons in an inflammatory environment. It has been concluded that targeting mitochondrial biogenesis to alleviate mitochondrial dysfunction holds significant potential for treating PD and other mitochondria-related diseases.[184]

Melatonin-loaded human serum albumin nanoparticles (MT@HSAnps) have been reported to enhance both mitophagy (removing depolarized mitochondria) and mitochondrial biogenesis. Hence, their potential as neurotherapeutic agents has been investigated.[180] The data in Fig. 8A indicate that MT@HSAnps prevent rotenone-induced PD by enhancing BMI1-mediated PTEN degradation and inducing mitochondrial autophagy. Mitophagy was assessed through colocalization analysis of mitochondria and lysosomes using confocal scanning microscopy (Fig. 8B). The rotenone-treated group exhibited reduced mitophagy, which was reversed in MT@HSAnp-cotreated cells. However, additional PRT4165 (a

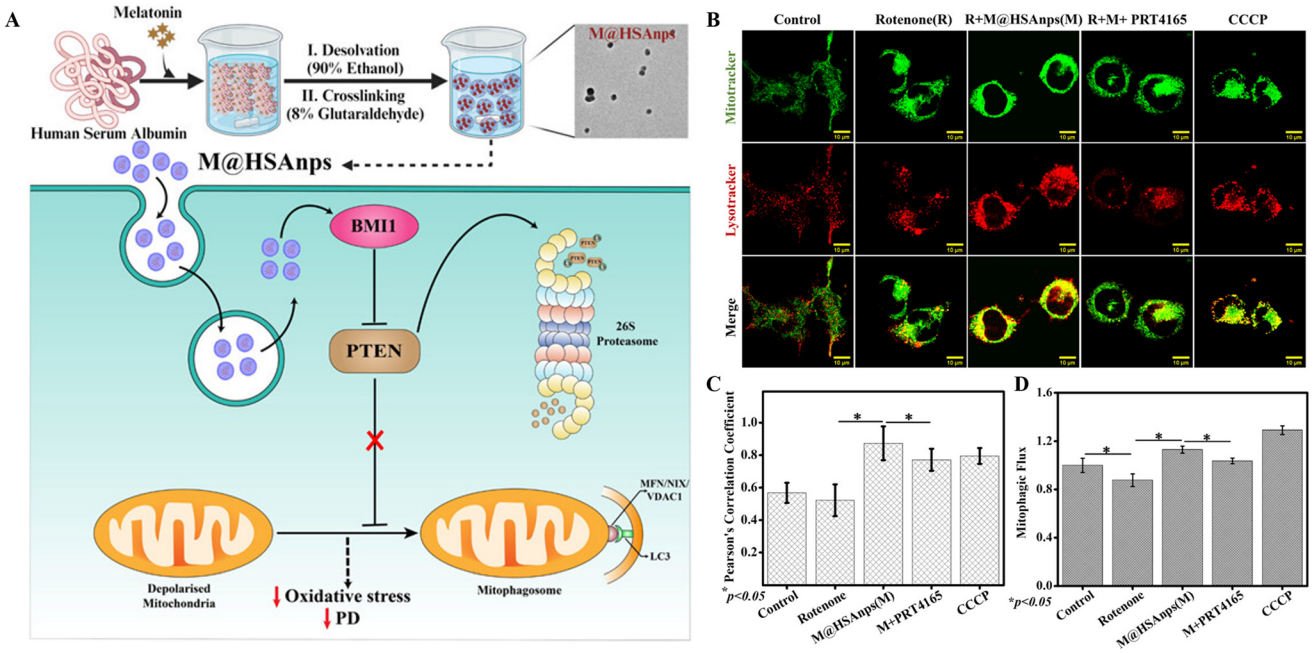

Fig. 8 (A) Schematic diagram of the preparation method of melatonin-loaded human serum albumin nanoparticles (M@HSAnps) and their mechanism of action exploiting enhanced mitophagy to alleviate PD (B–D). Evaluation of mitophagy: (B) confocal microscopy to analyze mitophagy, where MitoTracker and LysoTracker were used to stain the mitochondria and lysosomes, respectively. (C) Analysis of colocalization of mitochondria and lysosomes represented through the Pearson's correlation coefficients. (D) Estimation of the fold change in the mitophagic flux using a flow cytometer[180] (reproduced with permission from ref. 180. Copyright © 2024, American Chemical Society).

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chemical inhibitor of BMI1) cotreatment with MT@HSAnps hindered the effect of nanoformulation and inhibited mitophagy (Fig. 8B and C). Furthermore, the PRT4165 treatment group showed relatively lower mitophagy compared with the untreated control group. Considering that the downregulation of BMI1 inhibited mitophagy, it has been suggested as a novel crucial regulator of mitophagy (Fig. 8A). Mitophagic flux, an important parameter for assessing both the formation of mitophagosomes and their degradation in the lysosomes, was quantified by flow cytometry using MitoTracker Green FM and hydroxychloroquine (HCQ). It was established that MT@HSAnp cotreatment enhanced the flux, which was diminished by rotenone treatment (Fig. 8D).

The development of MT-based nanomedicines accounts also for the fact that the neurological disorders are multifactorial. Nanomedicines that can act on multiple molecular targets comprise a promising strategy to halt the progression of these diseases. Combination therapies can be envisioned by synthesizing new compounds that exert diverse activities. For example, a series of MT–alkylbenzylamine hybrids have been designed and synthesized as multitarget agents for the treatment of AD.[185] However, the development of novel drugs is a long and costly path. Hence, straightforward combining of existing drugs, by encapsulating them in the same nanocontainer, presents an intriguing alternatove.[186]

Recently, smart nanocomplexes have been fabricated by combining targeted and multi-drug properties. Fig. 9 presents nanospheres for the targeted delivery of acetylcholine and MT *via* a C5a-targeted aptamer which effectively reduces the reperfusion injury in ischemic stroke. The SiO_2@PAA-MT/ACh-aC5a nanospheres, guided by anti-C5a aptamers, were administered *via* intravenous injection and were found to cross the damaged BBB to target ischemic regions. Additionally, the specific binding of anti-C5a aptamers to C5a selectively reduced C5a-mediated inflammatory cytokines from microglia. Importantly, the low pH in ischemic regions triggered the release of acetylcholine (ACh) and MT molecules, which polarize microglia from the M1 to M2 phenotype, thereby suppressing the inflammatory response, and eliminating reactive oxygen species (ROS) to alleviate oxidative stress. This approach may enable the SiO_2@PAA-MT/ACh-aC5a nanospheres to ultimately protect neurons from inflammatory damage and oxidative stress in cerebral ischemia–reperfusion injury.[187]

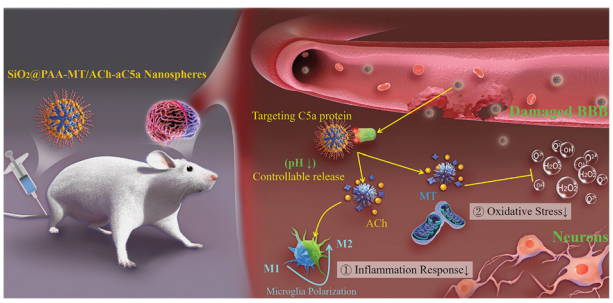

Fig. 9 Schematic illustration of cerebral ischemia/reperfusion injury treatment with SiO_2@PAA-MT/ACh-aC5a biocompatible nanospheres to attenuate the inflammatory response and oxidative stress on neurons in vivo[187] (reproduced with permission from ref. 187. Copyright © 2023, Wiley).

4.3 Lipid liquid crystalline nanoparticles as promising CNS drug delivery vehicles

Lyotropic lipid liquid crystalline nanoparticles (LCNPs) comprise an advanced class of nanomaterials for drug delivery. They are the next generation of bilayer membrane structures forming more complex 2D- and 3-dimensional nonlamelllar architectures that may involve inverted cubic and hexagonal mesophase inner organizations.[188] Compared with liposomal drug delivery nanocarriers, lipid-based cubosomes, hexosomes and spongosomes involve multiple internal compartments, which represent a structural advantage enabling an enhanced encapsulation efficacy. The entrapment of biomolecules of various sizes and hydrophilicities can be achieved as well as sustained drug release.[189] Selachyl alcohol-based cubosome and hexosome LCNPs have demonstrated high encapsulation efficiencies for the model anti-seizure drug phenytoin, exceeding 97% in both types of particle. For this type of drug, cubosomes proved to be more effective than hexosomes for delivering the therapeutic molecules to the brain, highlighting the significant potential of cubosomes as LCNPs for drug delivery.[190]

Nonlamellar liquid crystalline organizations and topologies have been proved as favorable for the encapsulation of various types of therapeutic compound (anti-viral, anti-oxidant, antibiotic, anti-cancer, *etc.*) of interest for nanomedicine development.[191,192] Lipid nanocarriers have attracted considerable attention in the field of neuroprotection and neuro-regeneration as delivery vehicles through the BBB.[193,194] LCNPs enhanced the nose-to-brain delivery of lipophilic drugs such as tranilast,[195] plasmalogens,[196] duloxetine hydrochloride,[197] and hydrophilic drugs such as almotriptan malate.[198] Curcumin, fish oil, and BDNF have been successfully co-encapsulated in monoolein-based cubosome and spongosome LCNPs and have shown *in vitro* neuroprotective potential to alleviate endoplasmic reticulum stress.[199] Vesicular and nonlamellar-type LCNPs, and lipid–peptide nanocarriers encapsulating a PUFA-plasmalogen and a neurotrophic peptide, have been shown to promote neuronal cell regeneration after oxidative stress through a survival mechanism involving CREB phosphorylation.[200]

5 Conclusions

MT exerts neuroprotective, neuromodulatory, antioxidant, anti-inflammatory, and anti-aging properties, but has poor pharmacological characteristics. MT-loaded nanocarriers, compared with a free MT drug, have demonstrated superior antioxidant, anti-inflammatory, and neuroprotective activities across various cell types and biological tissues. Among the reported nanocarrier systems, lipid nanocarriers have received

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significant interest due to their solubilizing properties, drug protective potential, biocompatibility, tolerability, and ability to bypass physiological barriers. Strategies such as multi-drug loading, targeted delivery, and multifunctionality can enhance the potential of MT-based nanomedicines to exert neuroprotective and neuro-regenerative effects. While various nanosystems have been utilized for MT encapsulation and delivery, LCNPs stand out as promising CNS drug delivery vehicles, offering advantages like enhanced stability, controlled release, improved bioavailability, and reduced undesirable side effects. These characteristics make LCNPs particularly beneficial for brain-targeted MT delivery in view of the treatment of neurological diseases. Therefore, MT-loaded LCNPs may provide a novel avenue in preventing and treating neurological disorders, thus necessitating further research to substantiate this potential.

Abbreviations

AC	Adenylyl cyclase
ACE2	Angiotensin-converting enzyme 2
ACh	Acetylcholine
AD	Alzheimer's disease
Akt/PKB	Protein kinase B
AmB	Amphotericin B
ANA12	An antagonist of the TrkB receptor
ATF6	Transcription factor 6
ATP	Adenosine triphosphate
Aβ	Amyloid-β
Bax	Bcl2-associated X protein
BBB	Blood–brain barrier
Bcl2	B-cell lymphoma 2
BDNF	Brain-derived neurotrophic factor
BH3	Bcl-2 homology 3 domain
Bmal1	Brain and muscle aryl hydrocarbon receptor nuclear translocator-like 1
C/EBP	CCAAT/enhancer binding protein
Ca^{2+}	Calcium ions
CaMKII	Calcium/calmodulin-dependent protein kinase II
cAMP	Cyclic adenosine monophosphate
CAT	Catalase
CC	Cerebral cortex
CCT	Capric/caprylic triglyceride
CD206	Cluster of differentiation 206
CDK5	Cyclin-dependent kinase 5
cGAS	Cyclic GMP-AMP synthase
cGMP	Cyclic guanosine monophosphate
CHOP	C/EBP homologous protein
CNS	Central nervous system
COX-2	Cyclooxygenase-2
CPK	Creatine phosphokinase 4
CREB	cAMP response element-binding protein
CRP	C-reactive protein 1
CsA	Cyclosporine A
DMPC	Dimyristoyl phosphatidyl choline
Drp1	Dynamin-related protein 1
ER	Endoplasmic reticulum
ERK1/2	Extracellular signal-regulated kinases 1 and 2
ESR	Erythrocyte sedimentation rate
ET	Ethosome
ET-LP	Ethanolic liposomes
Fe^{3+}	Ferric iron
FOXO3a	Forkhead box protein O3
Fth1	Ferritin heavy chain 1
GADD153	Growth arrest- and DNA damage-inducible gene 153
Gi/o proteins	G-protein alpha inhibitory/other subunits
Gpx4	Glutathione peroxidase 4
GRP78/BiP	Glucose-regulated protein 78/binding immunoglobulin protein
GSH-Px	Glutathione peroxidase
GSK3	Glycogen synthase kinase 3
H_2O_2	Hydrogen peroxide
HD	Huntington's disease
HDAC3	Histone deacetylase 3
Ho1	Heme oxygenase 1
HPMC	Hydroxypropyl methylcellulose
HSF1	Heat shock factor-1
HSP70	Heat shock protein 70
i.p.	Intraperitoneal injection
i.v.	Intravenous injection
IL-1β	Intereukin-1β
IL-6	Interleukin-6
iNOS	Inducible nitric oxide synthase
IP3	Inositol trisphosphate
IRE1	Inositol-requiring enzyme 1
JAK2	Janus kinase 2
JEV	Japanese encephalitis virus
KIF5A	Kinesin family member 5A
LC3-II	Microtubule-associated protein 1 light chain 3-II
LCNPs	Lipid lyotropic liquid crystalline nanoparticles
LDH	Lactate dehydrogenase3
LNC	Lipid nanocasules
LP	Liposomes
LPHNPs	Lipid–polymer hybrid nanoparticles
MAPK	Mitogen-activated protein kinase
MCAO	Middle cerebral artery occlusion
MCT	Medium chain triglycerides
MDA	Malondialdehyde
Mfn2	Mitofusin 2
MPP+	1-Methyl-4-phenylpyridinium
MS	Multiple sclerosis
MT	Melatonin
MT1	Melatonin receptor 1
MT2	Melatonin receptor 2
mtDNA	Mitochondrial DNA
mTOR	Mammalian target of rapamycin
N.A.	Not applicable
N1-AFMK	N1-acetyl-N2-formyl-5-methoxykynuramine
NAD+	Nicotinamide adenine dinucleotide

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NAS	*N*-Acetylserotonin
NC	Nanocapsules
NE	Nanoemulsions
NF-κB	Nuclear factor kappa B
NLCs	Nanostructured lipid carriers
NLRP3	NOD-like receptor family pyrin domain containing 3
NMDAR	*N*-Methyl-D-aspartate receptor
NOD	Domain nucleotide-binding oligomerization
NOS-2	Nitric oxide synthase 2
NPs	Nanoparticles
Nrf2	Nuclear factor erythroid 2-related factor 2
NS	Niosomes
NS3	Nonstructural protein 3
NS5	Nonstructural protein 5
p53	Tumor protein p53
p62	Sequestosome 1
p-AMPK	Phospho-5′AMP-activated protein kinase
PC	Phosphatidyl choline
PCBs	Polychlorinated biphenyls
PCDA	10,12-Pentacosadiynoic acid
PCL	Polycaprolactone
p-CREB	Phospho-CAMP-response element-binding
PD	Parkinson's disease
PERK	Protein kinase RNA-like endoplasmic reticulum kinase
p-JNK	Phosphorylated c-Jun N-terminal kinase
PKA	cAMP-dependent kinase A/protein kinase C
PKG	cGMP-dependent kinases/protein kinase G
PLA	Polylactic acid
PLCβ	Phospholipase C beta
PLGA	Poly(lactic-*co*-glycolic acid)
p-P38	Phosphorylated P38 MAPK
PrPC	Cellular prion protein
PTEN	Phosphatase and tensin homolog
PVA	Polyvinyl alcohol
REM	Rapid eye movement (sleep disorder)
RNS	Reactive nitrogen species
ROA	Route of administration
ROR	Retinoic acid-related orphan receptor
ROS	Reactive oxygen species
RZR	Retinoid Z receptor
s.c.	Subcutaneously
SCN	Suprachiasmatic nucleus
Sec. 62	Sec. 62 receptor (related to ER-phagy)
Sirt1	Sirtuin 1
SLNs	Solid lipid nanoparticles
SOD	Superoxide dismutase
STAT3	Signal transducer and activator of transcription 3
TD	Transdermal administration
TF	Transfersomes
TGFβ	Transforming growth factor-beta
THC	Δ9-Tetrahydrocannabinol
TLRs	Toll-like receptors
TMPRSS2	Transmembrane protease, serine 2
TNF-α	Tumor necrosis factor-α
TPP	Tripolyphosphate
VEGF	Vascular endothelial growth factor
$^{\bullet}$OH	Hydroxyl radicals
4P-PDOT	4-Phenyl-2-propionamidotetralin

Author contributions

Fucen Luo: investigation, visualization, writing – original draft, writing – review & editing; Yuru Deng: writing – review & editing; Borislav Angelov: funding acquisition, writing – review & editing; Angelina Angelova: conceptualization, supervision, project administration, writing – review & editing.

Data availability

No primary research results, software, or code have been included and no new data were generated or analyzed as part of this review.

All cited data were included in the article.

Conflicts of interest

There are no conflicts of interest to declare.

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