Review Article

The Potential Role of Melatonin on Memory Function: Lessons from Rodent Studies

(pineal gland / melatonin / learning / memory / rodents)

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Abstract. Pineal melatonin biosynthesis is regulated by the circadian clock located in the suprachiasmatic nucleus of the hypothalamus. Melatonin has been found to modulate the learning and memory process in human as well as in animals. Endogenous melatonin modulates the process of newly acquired information into long-term memory, while melatonin treatment has been found to reduce memory deficits in elderly people and in various animal models. However, the mechanisms mediating the enhancing effect of melatonin on memory remain elusive. This review intends to explore the possible mechanisms by looking at previous data on the effects of melatonin treatment on memory performance in rodents.

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Abbreviations: Aβ – β-amyloid, AβPP – Aβ precursor protein, AD – Alzheimer's disease, AFMK – N1-acetyl-N2-5-methoxykynuramine, BDNF – brain-derived neurotrophic factor, CaMKII – Ca^{2+}/calmodulin-dependent protein kinase II, ChAT – choline acetyltransferase, CREB – cyclic AMP-responsive element-binding protein, DEX – dexamethasone, DS – Down syndrome, GCLC – glutamate cysteine ligase catalytic, GPCR – G protein-coupled receptor, GPx – glutathione peroxidase, GSH – oxidized glutathione, HO-1 – haem oxygenase-1, i.p. – intraperitoneally, LPO – lipid peroxide, LPS – lipopolysaccharide, LTP – long-term potentiation, MDA – malondialdehyde, NF-κB – nuclear factor κB, NCAM – neural cell adhesion molecules, NO – nitric oxide, NR2B – N-methyl-D-aspartate receptor subtype 2B, Nrf2 – nuclear factor erythroid 2-related factor 2 (Nrf2), OKA – okadaic acid, ROS/RNS – reactive oxygen/nitrogen species, SCN – suprachiasmatic nucleus, SD – sleep deprivation, SOD – superoxide dismutase, STZ – streptozotocin, Tg – transgenic.

Introduction

Endogenous melatonin secretion is regulated by the circadian clock and by light/dark cycles. LeGates et al. (2014) propose indirect and direct influence of light on mood and learning. Through an indirect pathway, light influences sleep and secondarily influences mood and hippocampal-dependent learning. Light can also influence the mood and learning directly, independent of circadian arrhythmicity or sleep disruption. Inhibition of melatonin synthesis by the circadian clock or light directly facilitates long-term memory formation. Alternatively, the night-time peak in melatonin levels imposes an inhibitory effect on memory consolidation (Rawashdeh and Maronde, 2012).

However, exogenous melatonin has been found to be beneficial in improving certain aspects of cognitive function in elderly people (Peck et al., 2004), in various animal models such as Alzheimer's disease (AD) (Xian et al., 2002; Feng et al., 2004; Olcese et al., 2009; Eltablawy and Tork, 2014; Rudnitskaya et al., 2014; O'Neal-Moffitt et al., 2015), Down syndrome (DS) (Corrales et al., 2013), sleep deprivation (SD) (Zhang et al., 2013; Alzoubi et al., 2015; Kwon et al., 2015), and in various chemically induced memory impairments (Baydas et al., 2005a, b; Gönenç et al., 2005). In addition, the physiological melatonin levels were found to be significantly reduced in patients with AD (Skene et al., 1990; Mishima et al., 1999; Swaab, 2003; Wu et al., 2003). A recent publication revealed significant association between higher physiological melatonin levels with lower prevalence of cognitive impairment and depressed mood in a prospective community-based cohort study. The study subjects were 1127 community dwelling elderly subjects (age ≥ 60 years) voluntarily enrolled in the Housing Environments and Health Investigation among Japanese Older People in Nara, Kansai Region/HEIJO-KYO (Obayashi et al., 2015).

The therapeutic roles of melatonin in insomnia, mood disorders and AD have been extensively studied (Srinivasan et al., 2012a, b; 2014). However, the mechanisms mediating the enhancing effect of melatonin on memory formation are still elusive. This review intends to ex-

Table 1. Effects of melatonin treatment on memory and learning performance in rodents

Model	Animal used	Dose of melatonin	Effect on memory and learning	Reference
DS model	5- to 6-month-old Ts65Dn mice	0.5 mg/day (orally) for 5 months	Melatonin improved spatial learning and memory (Morris water maze) of both DS and control mice.	Corrales et al., 2013
AD model	4-month-old APP 695 transgenic (Tg) mice	10 mg/kg/day (orally) for 4 months	Melatonin alleviated learning and memory deficits (passive avoidance tests) of APP 695 Tg mice.	Feng et al., 2004
	2–2.5-month-old APP + PS1 double Tg mice	100 mg/l drinking water/day for 5 months	Melatonin protected from cognitive impairment in a variety of tasks of working memory, spatial reference learning/memory, and basic mnemonic function in double Tg mice.	Olcese et al., 2009
	1.5-month-old male senescence-accelerated OXYS rats	0.04 mg/kg/day (orally) for 2.5 months	Melatonin treatment of OXYS rats slowed down deterioration of reference memory (8-arm radial maze test).	Rudnitskaya et al., 2014
	4-month-old AβPP^{swe}/PSEN1dE9 double mutant Tg mice	0.5 mg/day in drinking water for 8–11 months	Melatonin significantly reduced cognitive deficits in a variety of tasks of spatial (Barnes maze and Morris water maze) and non-spatial (novel object recognition) learning of double mutant Tg mice.	O'Neal-Moffitt et al., 2015
	TG2576 mice	10 mg/kg/day (i.p.) for 8–12 months	Melatonin improved the memory deficit (Morris water maze, passive avoidance test) of TG 2576 mice.	Peng, 2015
	Adult rats AD was induced by injection of Aβ 25 ~ 35 into the hippocampus	0 1, 1, and 10 mg/kg/day (intragastric) for 10 days	Melatonin improved the cognitive function (Morris water maze) of Aβ 25 ~ 35 treated rats.	Xian et al., 2002
	Adult rats AD was induced by i.p. injection of LPS	10 mg/kg (i.p.) given 5 days/week for 6 weeks	Melatonin improved working memory (T maze) of LPS-induced AD rats.	Eltablawy et al., 2014
	Adult rats AD was induced by bilateral injection of Aβ peptides into the frontal cortices	30 mg/kg/day (i.p.) for 10 days	Melatonin did not prevent memory decline (passive avoidance test) in AD rats.	Eslamizade et al., 2016
SD model	Adult rats	15 mg/kg/day (i.p.) between 7:00 and 8:00	Melatonin reversed cognitive impairment (open field test and Morris water maze) in SD rats.	Zhang et al., 2013
	Adult rats	100 mg/kg/day (orally) for 4 weeks	Melatonin prevented memory impairment (radial arm water maze) in SD rats.	Alzoubi et al., 2015
	Adult rats	10 mg/kg/day. (i.p.) for 1 week	Melatonin treatment normalized memory impairment (Morris water maze) in SD rats to control levels.	Kwon et al., 2015
Chemically induced memory deficit model	Adult rats Ethanol 2.5 g/kg was diluted to 15 % in saline (i.p) 30 min before the first training session	10 mg/kg/day (i.p.) 15 min before the ethanol injections	Melatonin alone had a positive effect on cognition (Morris water maze performances) in ethanol-treated rats.	Gönenç et al., 2005
	Adult rats Ethanol 2 g/kg/day, (i.p.) for 45 days	10 mg/kg/day (i.p.) for 45 days	Melatonin improved learning and memory deficits (Morris water maze, passive avoidance and probe trial) in ethanol-treated rats. The impact of melatonin in preventing learning and memory deficits was higher in aged than young animals.	Baydas et al., 2005a
	Adult rats Thinner (3000 ppm 1 h/day) for 45 days	10 mg/kg/day (i.p.) for 45 days	Melatonin prevented learning and memory deficits (Morris water maze, passive avoidance and probe trial) caused by thinner inhalation.	Baydas et al., 2005b
	Adult rats Thinner inhalation (1 h per day) for 45 days	10 mg/kg/day (i.p.) for 45 days	Melatonin prevented learning and memory deficits (Morris water maze and probe trial) caused by thinner inhalation.	Nedzvetskii et al., 2012

Chemically induced memory deficit model	Adult rats Okadaic acid 200 ng (ICV)	Melatonin (20 mg/kg/day) and *Bacopa monnieri* (40 and 80 mg/kg/day) administered orally for 13 days	Treatment with *Bacopa monnieri* and melatonin significantly improved okadaic acid-induced memory dysfunction (Morris water maze).	Dwivedi et al., 2013
	Adult mice 0.3 ml of 1% D-galactose/mouse from days 7 to 56	10 mg/kg/day (orally) for 88 days	Ergothioneine and melatonin effectively protected against learning and memory deficits (active avoidance task and Morris water maze) in D-galactose-treated mice.	Song et al., 2014
	Adult rats D-galactose 100 mg/kg (i.p.) for 60 days	10 mg/kg/day (i.p.) for 30 days	Melatonin attenuated memory impairment (Morris water maze and Y-maze test) in D-galactose-treated rats.	Ali et al., 2015
	2-month-old mice Long-term anaesthesia using 1% isoflurane from circadian time 14 to 20	10 mg/kg/day (intragastrically) for 7 days	Melatonin pre-treatment improved isoflurane-induced spatial memory impairment.	Xia et al., 2016
	Adult rats 0.2% lead acetate solution from their birth day	3 mg/kg (gastric lavage) for 60 days	Melatonin exacerbated LTP impairment, learning and memory deficit (Morris water maze) in lead-exposed rats.	Cao et al., 2009
	Adult rats STZ at 3 mg/kg (icv)	10 mg/kg/day (i.p.) + dietary restriction	Melatonin and luzindole could not restore STZ-induced memory impairment (Morris water maze).	Mehdipour et al., 2015
	Adult mice Chronic administration of high doses (60 mg/kg) of dexamethasone (DEX) for 21 days	10 mg/kg/day (i.p.) 30 min before 0.9% normal saline or DEX treatment	Melatonin pre-treatment prevented DEX-induced cognitive impairment (Morris water maze).	Tongjaroenbuangam et al., 2013
	Adult rats 10 mg/kg DEX (i.p.)	40 mg/kg/day + Vit C 100 mg/kg/day for 9 days	Melatonin and Vit C failed to reverse DEX-induced learning and memory losses (radial arm maze test).	Yilmaz et al., 2015

plore the possible mechanisms by looking at previous data on the effects of melatonin treatment on memory performance in rodents (Table 1).

Melatonin

Melatonin is synthesized mainly in the pineal gland of all mammals including man. Tryptophan, which is taken up from the blood, serves as the precursor for melatonin biosynthesis. Melatonin in the plasma, blood and circulating fluids exhibits a characteristic circadian rhythm with very high nocturnal and low diurnal levels (Arendt, 2000). Pineal melatonin biosynthesis is regulated by the circadian clock located in the suprachiasmatic nucleus (SCN) of the hypothalamus and is entrained to the light-dark cycle through the retina-hypothalamic tract (Moore, 1996). Once formed in the pineal gland, melatonin is released immediately into the blood and its half-life is less than 30 min.

Melatonin is metabolized mainly in the liver via hydroxylation in the C6 position by cytochrome P450 monooxygenases (CYP1A2 and CYP1A1). It is then conjugated with sulphate to form 6-sulphatoxymelatonin. In the central nervous system, melatonin is metabolized to form kynuramine derivative N1-acetyl-N2-5-methoxykynuramine (AFMK) (Hirata et al., 1974). Melatonin can readily pass through all cell membranes, including the blood-brain barrier (Reiter et al., 1993). Its binding sites exist in various brain structures such as the hippocampus and prefrontal cortex (Weaver et al., 1989; Pandiperumal et al., 2008), known to play important roles in memory function (Mazzuchelli et al., 1996; Brzezinski, 1997; Savaskan et al., 2001, 2005; Ekmekçioğlu, 2006).

Physiological and pharmacological effects of melatonin are mostly manifested via its effects on membrane-bound melatonin receptors (MT1 and MT2) that occur in almost all tissues in the body. These melatonin receptors belong to the superfamily of G protein-coupled receptors (GPCrs) (Reppert et al., 1994, 1995). Another melatonin receptor known as MT3 is identified as an analogue of quinine reductase type-2 (Nosjean et al., 2000). Melatonin also binds to cytosolic proteins such as the calcium-binding protein, calmodulin or tubulin (Benitez-King, 2006). The nuclear receptors for melatonin, i.e. RORα1, RORα2 and RZRβ, all belong to the retinoic acid superfamily (Wiesenberg et al., 1998).

Animal Models

Down syndrome model

Melatonin was administered for five months to 5- to 6-month-old Ts65Dn mice, the most commonly used Down syndrome (DS) model. Melatonin treatment improved spatial learning and memory, and increased the number of choline acetyltransferase (ChAT)-positive

cells in the medial septum of both DS and control mice. However, melatonin treatment did not significantly reduce β-amyloid (Aβ) precursor protein (AβPP) or Aβ levels in the cortex or hippocampus of DS mice. The authors concluded that chronic melatonin supplementation may be an effective treatment for delaying age-related progression of cognitive deterioration found in DS individuals (Corrales et al., 2013).

Alzheimer's disease model

The long-term influence of oral melatonin (10 mg/kg) on behaviour, biochemical and neuropathological changes was evaluated in heterozygous transgenic (Tg) mice (APP 695 Tg in C57BL/6 background) and non-Tg mice. Melatonin was found to alleviate learning and memory deficits, increase ChAT activity in the frontal cortex and hippocampus, reduce the number of apoptotic neurons and decrease Aβ deposits in the frontal cortex of APP 695 Tg mice. Thus, the neuroprotective effects of melatonin could be related to modulation of apoptosis and the cholinergic system (Feng et al., 2004).

In a later study, Olcese et al. (2009) investigated the potential long-term melatonin treatment to protect against cognitive impairment and development of Aβ neuropathology. Melatonin (100 mg/l) was administered in drinking water to APP + PS1 double transgenic (Tg) mice from 2–2.5 months to 7.5 months of age. Mice treated with melatonin were protected from cognitive impairment in a variety of tasks such as working memory, spatial reference learning/memory, and basic mnemonic function. The melatonin cognitive benefits possibly involve its anti-Aβ aggregation, anti-inflammatory, and/or antioxidant properties. This lends support for long-term melatonin therapy as a primary or complementary strategy for abating progression of AD.

Similarly, oral melatonin at a dose of 0.04 mg per kg body weight per day administered at the age of active progression of AD-like pathology (i.e. from age 1.5 months to 4 months) decreased the amyloid-β1-42 and amyloid-β1-40 levels in the hippocampus and amyloid-β1-42 levels in the frontal cortex. Melatonin slowed down degenerative alterations in hippocampal neurons especially in the CA1 region as well as deterioration of reference memory of senescence-accelerated OXYS rats. Melatonin also prevented decrease in the mitochondria-occupied portion of the neuronal volume and improved the ultrastructure of mitochondria in the neurons of the CA1 region in the hippocampus (Rudnitskaya et al., 2014).

Recent studies reported the prophylactic role of melatonin in reducing AD neuropathology (O'Neal-Moffitt et al., 2015) and in increasing expression of synapse-associated proteins (synaptophysin). It also increases memory-associated early response genes (*arc* and c-*fos*) as well as cyclic AMP-responsive element-binding protein (CREB) in hippocampus extracts (Peng, 2015). These findings suggest the role of melatonin in synaptic connections and molecular pathways leading to memory formation.

Apart from using transgenic animals, an AD model was also developed in adult rats by injecting Aβ peptides or lipopolysaccharide (LPS). Melatonin was found to improve cognitive functions (Xian et al., 2002; Eltablawy and Tork, 2014), increase the number/activity of ChAT in the brain (Xian et al., 2002; Eltablawy and Tork, 2014), improve function of mitochondria (Eltablawy and Tork, 2014), and prevent Aβ-induced increase in nuclear factor κB (NF-κB) from immunoreaction and shrinkage of the CA1 pyramidal neurons (Eslamizade et al., 2016).

Sleep deprivation model

The SD animal model impairs both short- and long-term memory. Melatonin plays a significant neuroprotective role in repairing the cognitive impairment, reversing the levels of oxidative stress markers including nitric oxide (NO), malondialdehyde (MDA) and superoxide dismutase (SOD), reducing catalase and glutathione peroxidase (GPx) activities, and improving the relative protein levels of Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII) and brain-derived neurotrophic factor (BDNF) in cerebral cortex and hippocampal CA1, CA3 and DG regions (Zhang et al., 2013; Alzoubi et al., 2015). Melatonin treatment not only normalizes memory impairment and oxidative stress, but also causes glial activation and decreases fragile X-mental retardation protein expression in the neurons to control levels (Kwon et al., 2015). This fragile X protein has been shown to regulate circadian rhythms and memory in flies (Dockendorff et al., 2002; Inoue et al., 2002; McBride et al., 2005; Bolduc et al., 2008) and mice (Zhao et al., 2005, Zhang et al., 2008).

Chemically Induced Memory Impairment

Gönenç et al. (2005) investigated the effect of melatonin against ethanol-induced oxidative stress and spatial memory impairment in rats. Ethanol was diluted to 15 % in saline and administered intraperitoneally (i.p.) 30 min before the first training session on each day of the spatial memory tasks (Acheson et al., 2001). Melatonin had positive effects on water maze performances but not on ethanol-induced spatial memory impairment.

Baydas et al. (2005a) compared the effects of melatonin on ethanol-induced memory deficits in young and aged rats. Melatonin improved learning and memory deficits, possibly by inhibiting oxidative stress via reducing lipid peroxide (LPO) and elevating oxidized glutathione (GSH) levels, and by modulating neural plasticity as evidenced by neural cell adhesion molecule (NCAM) expression in the hippocampus. The impact of melatonin in preventing learning and memory deficits was, however, higher in aged compared to young animals.

Melatonin treatment also prevents thinner-induced learning and memory deficits in rats (Baydas et al., 2005b; Nedzvetskii et al., 2012). Learning and memory deficits were caused by inhalation of high concentrations (3000 p.p.m.) of the thinner for 1 h a day for 45 days. Melatonin increased NCAM in the hippocampus, cortex, and cerebellum and reduced LPO (malondialdehyde and 4-hydroxyalkenals) in these cerebral structures

(Nedzvetskii et al., 2012). Both studies concluded that the beneficial effects of melatonin could possibly be due to the reduction in oxidative stress and normalization of neural plasticity.

Dwivedi et al. (2013) induced memory dysfunction using okadaic acid (OKA) and found that melatonin significantly improved memory dysfunction in OKA rats and restored nuclear factor erythroid 2-related factor 2 (Nrf2), haem oxygenase-1 (HO-1), and glutamate cysteine ligase catalytic subunit (GCLC) expression. These factors work together to strengthen cellular defence and scavenge reactive oxygen/nitrogen species (ROS/RNS) and detoxify electrophiles (Lee et al., 2003; Satoh et al., 2008).

In a recent study, D-galactose was administered to induce memory impairment (Song et al., 2014; Ali et al., 2015), synaptic dysfunction and oxidative stress through decreasing 8-oxoguanine, and inhibiting RAGE/NF-κB/JNK-mediated inflammation and neurodegeneration (Ali et al., 2015). Melatonin treatment (10 mg/kg, i.p.) alone or in combination with ergothioneine was able to reverse D-galactose-induced synaptic disorder via attenuation of oxidative damage and restoration of memory (Song et al., 2014; Ali et al., 2015).

A more recent study by Xia et al. (2016) showed that pre-treatment with melatonin ameliorated a disturbed sleep-wake cycle, improved isoflurane-induced spatial memory impairment, and reversed down-regulation of CREB and N-methyl-D-aspartate receptor subtype 2B (NR2B) expression. It is possible to suggest that the NR2B-CREB signalling pathway has a critical role in the memory process. Thus, hippocampus-specific elevation of the NR2B subunit composition enhances long-term potentiation (LTP) in CA1 neurons, which may produce hippocampal-dependent cognitive improvement after anaesthesia (Xia et al., 2016).

While many previous studies revealed beneficial effects of melatonin pre-treatment or treatment on memory functions, a few studies reported equivocal or even negative effects of melatonin on the memory function.

When melatonin was administered over a prolonged period to lead-exposed rats, it exacerbated lead-induced LTP impairment, learning and memory deficit (Cao et al., 2009). Thus, the authors concluded that melatonin is not suitable for healthy and lead-exposed children. Whether the LTP impairment in this animal model was associated with alteration in CREB2B expression (Yin et al., 1994, 1995; Tubon et al., 2013) and spared the short-term memory remains to be investigated.

In another study using streptozotocin (STZ) to induce memory deficits, melatonin seemed to have no important role in the effects of dietary restriction on spatial memory impairment. Similarly, melatonin and luzindole could not restore STZ-induced memory impairment, but were able to partially reduce the number of dead neurons in CA1 of the hippocampus (Mehdipour et al., 2015).

Melatonin showed inconclusive results when used in dexamethasone (DEX)-induced memory deficit animals. Pre-treatment with melatonin prior to the DEX treatment resulted in shorter escape latencies and longer remaining in the target quadrant compared to pre-treatment only with DEX. Melatonin also significantly prevented DEX-induced reduction in the expression of NR2A/B, BDNF, CaMKII and synaptophysin in mice (Tongjaroenbuangam et al., 2013). In another study, however, melatonin, when given together with vitamin C, failed to reverse the DEX-induced memory deficit in rats (Yılmaz et al., 2015).

Earlier studies using the AD model showed improvement in cognitive function (Xian et al., 2002). However, a study by Eslamizade et al. (2016) showed no effect of melatonin on the cognitive function despite its protective effects against Aβ-induced increased NF-κB and shrinkage of the CA1 pyramidal neurons. Differences between the previous reports and the study by Eslamizade et al. (2016) include differences in the melatonin dose, age of treatment initiation, and method of AD induction. In the study by Xian (2002) melatonin was administered intragastrically rather than intraperitoneally, and in doses ranging from 0.1 to 10 mg/kg/day for similar treatment duration.

Conclusion

Melatonin could be involved in stabilizing synaptic connections during memory and learning processes as well as in modulating expression of various proteins such as BDNF, NR2B, CREB, arc, c-fos and NCAM during memory formation. In addition, melatonin has anti-inflammatory and anti-amyloidogenic properties and is also an antioxidant. Therefore, it has the potential to reduce brain damage and improve learning and memory deficits.

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