Therapeutical Implications of Melatonin in Alzheimer’s and Parkinson’s Diseases

Daniel P. Cardinali *1, Daniel E. Vigo 1, Natividad Olivar2, María F. Vidal 1, Luis I. Brusco 2

Abstract Neurodegenerative diseases like Alzheimer’s disease (AD) and Parkinson’s disease (PD) are major health problems, and a growing recognition exists that efforts to prevent them must be undertaken by both governmental and nongovernmental organizations. In this context, the pineal product melatonin has a promising significance because of its chronobiotic/cytoprotective properties. One of the features of advancing age is the gradual decrease in endogenous melatonin synthesis. A limited number of therapeutic trials have indicated that melatonin has a potential therapeutic value as a neuroprotective drug in the treatment of AD, mild cognitive impairment (which may evolve to AD), and PD. Both in vitro and in vivo, melatonin prevented the neurodegeneration seen in experimental models of AD and PD. For these effects to occur, doses of melatonin about two orders of magnitude higher than those required to affect sleep and circadian rhythmicity are needed. More recently, attention has been focused on the development of potent melatonin analogs with prolonged effects which were employed in clinical trials in sleep-disturbed or depressed patients in doses considerably higher than those employed for melatonin. In view that the relative potencies of the analogs are higher than that of the natural compound, clinical trials employing melatonin in the range of 50–100 mg/day are needed to assess its therapeutic validity in neurodegenerative disorders.

Keywords Melatonin • Neurodegeneration • Free radicals • Oxidative stress • Aging • Parkinson’s disease • Alzheimer’s disease • Mild cognitive impairment • Melatonin analogs

1 Departamento de Docencia e Investigación, Facultad de Ciencias Médicas, Pontificia Universidad Católica Argentina, Argentina
*e-mail: danielcardinali@uca.edu.ar; danielcardinali@fibertel.com.ar

2 Centro de Neuropsiquiatría y Neurología de la Conducta, Hospital de Clínicas “José de San Martín”, Facultad de Medicina, Universidad de Buenos Aires, Buenos Aires, Argentina
### Abbreviations

| Abbreviation | Description |
|--------------|-------------|
| 6-OHDA       | 6-hydroxydopamine |
| Ach          | Acetylcholine |
| AChE         | Acetylcholinesterase |
| AD           | Alzheimer’s disease |
| AFMK         | N\(^1\)-Acetyl-N\(^2\)-formyl-5-methoxykynuramine |
| AMK          | N\(^4\)-Acetyl-5-methoxykynuramine |
| APP          | Amyloid precursor protein |
| A\(\beta\)   | Aggregated \(\beta\)-amyloid |
| Bel-2        | B cell lymphoma proto-oncogene protein |
| ChAT         | Choline acetyltransferase |
| Cox          | Cyclooxygenase |
| DA           | Dopamine |
| GABA         | \(\gamma\)-Aminobutyric acid |
| GPR50        | G-protein receptor 50 ortholog |
| GPx          | Glutathione peroxidase |
| GRd          | Glutathione reductase |
| GSH          | Reduced glutathione GSK–3 |
| iNOS         | Inducible nitric oxide synthase |
| l-DOPA       | l-Dihydroxyphenylalanine |
| MAO          | Monoamine oxidase |
| MAP          | Microtubule-associated protein |
| MCI          | Mild cognitive impairment |
| MCI          | Mild cognitive impairment |
| MPP\(+\)     | 1-Methyl-4-phenylpyridinium |
| MPTP         | 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine |
| mPTP         | Mitochondrial permeability transition pore |
| mRNA         | Messenger ribonucleic acid |
| MT\(_1\)     | Melatonin receptor 1 |
| MT\(_2\)     | Melatonin receptor 2 |
| MT\(_3\)     | Melatonin receptor 3 |
| NF\(\kappa\)B| Nuclear factor \(\kappa\)B |
| nNOS         | Neuronal nitric oxide synthase |
| NO           | Nitric oxide |
| PD           | Parkinson’s disease |
| PK           | Protein kinase |
| RBD          | REM-associated sleep behavior disorder |
| REM          | Rapid eye movement |
| RNS          | Reactive nitrogen species |
| ROR          | Retinoic acid receptor-related orphan receptor |
| ROS          | Reactive oxygen species |
| RZR          | Retinoid Z receptor |
| SCN          | Suprachiasmatic nuclei |
| SNpc         | Substantia nigra pars compacta |
| SOD          | Superoxide dismutase |
9.1 Introduction

Neurodegenerative disorders are a group of chronic and progressive diseases characterized by selective and symmetric losses of neurons in cognitive, motor, or sensory systems. Alzheimer’s disease (AD) and Parkinson’s disease (PD) are the most clinically relevant examples of neurodegenerative disorders. Although the origin of specific neurodegeneration in these disorders remains mostly undefined, three major and frequently interrelated processes, namely, free radical-mediated damage, mitochondrial dysfunction, and excitotoxicity, have been identified as common pathophysiological mechanisms for neuronal death (Reiter et al. 1998).

Neurodegenerative diseases have become a major health problem, and a growing recognition exists that efforts to prevent these diseases at an early stage of development must be undertaken by both governmental and nongovernmental organizations. Regular intake of antioxidants by the elderly has been recommended for prevention of age-associated, free radical-mediated, and neurodegenerative diseases, although the efficacy of this treatment is discussed (Johnson et al. 2013). In this context, the use of melatonin as a cytoprotective agent becomes of interest.

Melatonin is a well-preserved methoxyindole found in most phyla having remarkable cytoprotective actions in addition to chronobiotic properties. The source of circulating melatonin is the pineal gland, and a substantial amount of data support that plasma melatonin decrease is one of the features of advancing age (Bubenik and Konturek 2011). In this chapter we will first summarize the efficacy of melatonin to decrease basic processes of brain degeneration in animal models of AD and PD. We will then assess the clinical data that support the possible therapeutic efficacy of melatonin in AD and PD.

9.2 Basic Biology of Melatonin Relevant to Neurodegeneration

Tryptophan serves as the precursor for melatonin biosynthesis. It is hydroxylated at C5 position and then decarboxylated to form serotonin. Serotonin is N-acetylated by the enzyme serotonin-N-acetyl transferase and the produced N-acetylserotonin is finally O-methylated by the enzyme hydroxyindole-O-methyl transferase to form melatonin.

In all mammals, circulating melatonin derives primarily from the pineal gland (Claustrat et al. 2005). In addition, melatonin is locally synthesized in many cells, tissues, and organs including lymphocytes, bone marrow, thymus, gastrointestinal tract, skin, and eyes, where it may play either an autocrine or paracrine role (see for (Hardeland et al. 2011)). Both in animals and in humans, melatonin participates in diverse physiological functions signaling not only the length of the night but also enhancing free radical scavenging and the immune response, showing relevant cytoprotective properties (Hardeland et al. 2011).
Circulating melatonin binds to albumin (Cardinali et al. 1972) and is metabolized mainly in the liver where it is hydroxylated in the C6 position by the cytochrome P₄₅₀ monooxygenases A2 and 1A (Facciola et al. 2001; Hartter et al. 2001). Melatonin is then conjugated with sulfate to form 6-sulfatoxymelatonin, the main melatonin metabolite found in urine. Melatonin is also metabolized in tissues by oxidative pyrrole ring cleavage into kynuramine derivatives. The primary cleavage product is N\(^2\)-acetyl-N\(^5\)-formyl-5-methoxykynuramine (AFMK), which is deformatylated, either by arylamine formamidase or by hemoperoxidase, to N\(^1\)-acetyl-5-methoxykynuramine (AMK) (Hardeland et al. 2009). It has been proposed that AFMK is the primitive and primary active metabolite of melatonin to mediate cytoprotection (Tan et al. 2007). Melatonin is also converted into cyclic 3-hydroxymelatonin in a process that directly scavenges two hydroxyl radicals (Tan et al. 2007).

Melatonin exerts many physiological actions by acting on membrane and nuclear receptors while other actions are receptor independent (e.g., scavenging of free radicals or interaction with cytoplasmic proteins) (Reiter et al. 2009). The two membrane melatonin receptors cloned so far (MT\(_1\) and MT\(_2\)) have seven membrane domains and belong to the superfamily of G-protein-coupled receptors (Dubocovich et al. 2010). MT\(_1\) and MT\(_2\) receptors are found in the cell membrane as dimers and heterodimers. GPR50, a G-protein-coupled melatonin receptor ortholog that does not bind melatonin itself, dimerizes with MT\(_1\) receptors and can block melatonin binding (Levoye et al. 2006). The human MT\(_2\) receptor exhibits a lower affinity than the human MT\(_1\) receptor and becomes desensitized after exposure to melatonin, presumably by an internalization mechanism.

As representatives of the G-protein-coupled receptor family, MT\(_1\) and MT\(_2\) receptors act through a number of signal transduction mechanisms (Dubocovich et al. 2010). The MT\(_1\) receptor is coupled to G proteins that mediate adenyl cyclase inhibition and phospholipase C activation. The MT\(_2\) receptor is also coupled to the inhibition of adenyl cyclase, and it additionally inhibits the soluble guanylyl cyclase pathway.

By using receptor autoradiography with the nonselective 2-[\(^{125}\)I]iodomelatonin ligand and real-time quantitative reverse transcription–polymerase chain reaction to label melatonin receptor mRNA, MT\(_1\) and MT\(_2\) receptors have been identified in the retina, suprachiasmatic nuclei (SCN), thalamus, hippocampus, vestibular nuclei, and cerebral and cerebellar cortex. At the level of the hippocampus, MT\(_2\) receptors were detected in CA3 and CA4 pyramidal neurons, which receive glutamatergic excitatory inputs from the entorhinal cortex, whereas MT\(_1\) receptors were predominantly expressed in CA1.

In addition to binding to MT\(_1\) and MT\(_2\) receptors, melatonin has been shown to display affinity for another binding site, originally considered to represent a membrane-bound receptor (MT\(_3\)), but then confirmed to be an enzyme, quinone reductase 2 (QR2) (Nosjean et al. 2000). Polymorphisms in the promoter of the human QR2 gene are associated with PD and a decline in cognitive ability over time (Harada et al. 2001).
Melatonin also binds to transcription factors belonging to the retinoic acid receptor superfamily, in particular, splice variants of RORα (RORα1, RORα2, and RORα isoform d) and RZRβ (Wiesenbergen et al. 1995; Lardone et al. 2011). Retinoic acid receptor subforms are ubiquitously expressed in mammalian tissues, and relatively high levels were detected especially in T- and B-lymphocytes, neutrophils, and monocytes (Lardone et al. 2011).

Melatonin is a powerful antioxidant that scavenges *•OH radicals as well as other radical oxygen species (ROS) and radical nitrogen species (RNS) and that gives rise to a cascade of metabolites that share antioxidant properties (Galano et al. 2011). Melatonin also acts indirectly to promote gene expression of antioxidant enzymes and to inhibit gene expression of prooxidant enzymes (Antolin et al. 1996; Pobals et al. 1998; Rodriguez et al. 2004; Jimenez-Ortega et al. 2009). In particular, this holds for glutathione peroxidase (GPx) and for glutathione reductase (GRd), presumably in response to GPx-dependent increases in GSSG, the oxidized form of glutathione (GSH). Melatonin contributes to maintain normal brain GSH levels (Subramanian et al. 2007) by stimulating GSH biosynthesis via γ-glutamylcysteine synthase and glucose-6-phosphate dehydrogenase (Rodriguez et al. 2004; Kilanczyk and Bryszewska 2003).

As abovementioned, the antioxidative efficiency of melatonin is high because the metabolites formed after free radical scavenging also act as free radical scavengers with an activity even higher than the native compound. Melatonin has a demonstrated superiority to vitamin C and E in protection against oxidative damage and in scavenging free radicals (Galano et al. 2011). Additionally, melatonin potentiates effects by other antioxidants, such as vitamin C, Trolox (a water-soluble vitamin E analog), and NADH.

Melatonin has significant anti-inflammatory properties presumably by inhibiting nuclear factor κ B (NF κB) binding to DNA thus decreasing the synthesis of proinflammatory cytokines, by inhibiting cyclooxygenase (Cox) (Cardinali et al. 1980) particularly Cox-2 (Deng et al. 2006) and by suppressing inducible nitric oxide (NO) synthase (iNOS) gene expression (Costantino et al. 1998). Melatonin was shown to protect from oxidotoxicity already at physiological concentrations (Galano et al. 2011; Tan et al. 1994). Although melatonin’s direct action as an antioxidant agent is mostly independent on receptor interaction (Leon-Blanco et al. 2004), the upregulation of antioxidant enzymes involves nuclear transcription and in some cases RZR/RORα receptors (Urata et al. 1999).

The efficacy of melatonin in inhibiting oxidative damage has been tested in a variety of neurological disease models where free radicals have been implicated as being at least partial causal agents of the condition. Besides the animal models of AD and PD discussed below, melatonin has been shown to lower neural damage due to cadmium toxicity (Poliandri et al. 2006; Jimenez-Ortega et al. 2011), hyperbaric hypoxia (Shaikh et al. 1997; Pobals et al. 1997), δ-aminolevulinic acid toxicity (Princ et al. 1997; Carneiro and Reiter 1998; Onuki et al. 2005), γ radiation (Erol et al. 2004; Shirazi et al. 2011; Tayasi et al. 2008), focal ischemia (Lee et al. 2004; Tai et al. 2011), brain trauma (Benu et al. 2004; Tsai et al. 2011; Kabadi and Maher 2010), and a number of neurotoxins (Reiter et al. 2010).
Melatonin’s neuroprotective properties, as well as its regulatory effects on circadian disturbances, validate melatonin’s benefits as a therapeutic substance in the preventive treatment of neurodegenerative diseases discussed below. Moreover, melatonin exerts anti-excitatoty, and at sufficient dosage, sedating effects (Golombek et al. 1996; Caumo et al. 2009) so that a second neuroprotective mode of action may exist involving the γ-aminobutyric acid (GABA)-ergic system as a mediator. This view is supported by studies indicating that melatonin protects neurons from the toxicity of the amyloid-β (Aβ) peptide (a main neurotoxin involved in AD) via activation of GABA receptors (Louzada et al. 2004).

Melatonin has also anti-excitotoxic actions. Early studies in this regard employed kainate, an agonist of ionotropic glutamate receptors, and gave support to the hypothesis that melatonin prevents neuronal death induced by excitatory amino acids (Giusti et al. 1996; Manev et al. 1996). It has also been reported that administration of melatonin reduces the injury of hippocampal CA1 neurons caused by transient forebrain ischemia (Cho et al. 1997; Kilic et al. 1999) or high glucocorticoid doses (Furio et al. 2008).

The various types of toxicities listed above can result in cell death by necrosis or apoptosis. Apoptotic neuronal death requires RNA and protein synthesis and depletion of trophic factors. Apoptosis also involves single-strand breaks of DNA and neurotrophic factors have been found to rescue neurons from this type of death (Dodd et al. 2013). They may act via cellular antiapoptotic components, such as the B cell lymphoma proto-oncogene protein (Bcl-2). Bcl-2 is capable of blocking the apoptotic pathway in the mitochondria by preventing the formation of a functional mitochondrial permeability transition pore (mtPTP) and, thus, the release of the mitochondrial enzyme cytochrome c, which represents the final and no-return signal of the apoptotic program (Khandelwal et al. 2011). Studies in vitro indicate that melatonin enhances expression of Bcl-2 and prevents apoptosis (Jiao et al. 2004; Koh 2011; Radogna et al. 2010). In addition, melatonin directly inhibits the opening of the mtPTP, thereby rescuing cells (Peng et al. 2012; Jou 2011; Andrabi et al. 2004).

9.3 Basic Aspects of Melatonin Activity in Animal Models of AD

The pathological signature of AD includes extracellular senile plaques, formed mainly by Aβ deposits, and intracellular neurofibrillary tangles, resulting mainly from abnormally hyperphosphorylated microtubule-associated protein (MAP) tau. Aβ is generally believed to play an important role in promoting neuronal degeneration in AD turning neurons vulnerable to age-related increases in the levels of oxidative stress and an altered cellular energy metabolism. Concerning the microtubule-associated protein tau, it promotes microtubule assembly and is a major factor to stabilize microtubules.

Aβ is composed by 39–43 amino acid residues derived from its precursor, the amyloid precursor protein (APP) (Selkoe 2004). APP is proteolytically processed by α- or β-secretases in different pathways. The α-non-amyloidogenic pathway
involves cleavage of APP by α-secretase to release a fragment of APP N–terminal, which after cleavage by γ-secretase precludes the formation of Aβ (Selkoe 2004). The β-amyloidogenic pathway includes β-secretase which results in the formation of intact Aβ peptide and is mediated by the sequential cleavage of β-secretase and γ-secretase at the N- and C-terminal of Aβ sequence (Selkoe 2004). Melatonin inhibited the normal levels of soluble APP secretion in different cell lines interfering with APP maturation (Lahiri and Ghosh 1999). Additionally, the administration of melatonin efficiently reduces Aβ generation and deposition in vivo (Matsubara et al. 2003; Lahiri et al. 2004) and in vitro (Lahiri and Ghosh 1999; Song and Lahiri 1997; Zhang et al. 2004; Olivieri et al. 2001).

Generally, the results in transgenic mice support the view that melatonin regulates APP and Aβ metabolism mainly by preventing the pathology, with little anti-amyloid and antioxidant effects occurring after the deposition of Aβ. Thus, melatonin therapy in old Tg2576 mice starting at 14 months of age could not prevent additional Aβ deposition (Quinn et al. 2005) while a similar treatment starting at the 4th month of age was effective to reduce Aβ deposition (Matsubara et al. 2003). Since amyloid plaque pathology is typically seen in 10–12-month-old Tg2576 mice (Hsiao et al. 1996), the data point out to the effectiveness of melatonin in preventing amyloid plaque formation rather than afterwards.

How melatonin exerts its inhibitory effect on the generation of Aβ remains undefined. The proteolytic cleavage of APP by α-secretase pathway is regulated by many physiological and pathological stimuli particularly through protein kinase (PK) C activation and secretase-mediated cleavage of APP. The inhibition of glycogen synthase kinase-3 (GSK-3) and upregulation of c-Jun N-terminal kinase result in high activity of matrix metalloproteinases with increasing degradation of Aβ (Donnelly et al. 2008). GSK-3 interacts with presenilin-1, a cofactor of γ-secretase, the phosphorylation of GSK-3, by PKC leading to γ-secretase inactivation. Indeed, GSK-3 can be one of the common signaling pathways increasing Aβ generation and tau hyperphosphorylation, and melatonin could regulate APP processing through PKC and GSK-3 pathways.

Melatonin interacts with Aβ40 and Aβ42 and inhibits progressive β-sheet and/or amyloid fibrils (Poeggeler et al. 2001; Pappolla et al. 1998). This interaction between melatonin and Aβ appears to depend on structural melatonin characteristics rather than on its antioxidant properties, since it could not be mimicked by melatonin analogs or other free radical scavengers (Poeggeler et al. 2001). By blocking the formation of secondary sheets, melatonin not only reduces neurotoxicity but also facilitates peptide clearance by increasing its proteolytic degradation.

Oxidative stress plays a central role in Aβ-induced neurotoxicity and cell death. Accumulating data support that melatonin effectively protects cells against Aβ-induced oxidative damage and cell death in vitro (Feng et al. 2004a; Zatta et al. 2003) and in vivo (Matsubara et al. 2003; Feng et al. 2004a; Furio et al. 2002; Shen et al. 2002; Rosales-Corral et al. 2003). In cells and animals treated with Aβ, melatonin could exert its protective activity through an antioxidant effect, whereas in APP transfected cells and transgenic animal models, the underlying mechanism may involve primarily the inhibition of generation of β-leaves and/or amyloid fibrils. Aggregated Aβ generates ROS that produce neuronal death by damage of neuronal
membrane lipids, proteins, and nucleic acids. Protection from Aβ toxicity by melatonin was observed, especially at the mitochondrial level (Olcese et al. 2009; Dragicevic et al. 2011).

As far as the hyperphosphorylation of tau, it reduces tau capacity to prevent microtubule changes and the disruption of the cytoskeleton arrangement ensues (Brion et al. 2001; Billingsley and Kincaid 1997). Indeed, the extent of neurofibrillary pathology correlates with the severity of dementia in AD patients. The level of hyperphosphorylated tau is three to four times higher in the brain of AD patients than in normal adult brains (Khatoon et al. 1992; Iqbal et al. 2005). More than 30 serine or threonine phosphorylation sites have been identified in the brains of AD patients (Nelson et al. 2012).

Melatonin efficiently attenuates tau hyperphosphorylation by affecting protein kinases and phosphatases in a number of experimental models including exposure of N2a and SH-SY5Y neuroblastoma cells to wortmannin (Deng et al. 2005), calyculin A (Li et al. 2004, 2005; Xiong et al. 2011), and okadaic acid (Benitez-King et al. 2003; Montilla-Lopez et al. 2002; Montilla et al. 2003; Wang et al. 2004). Melatonin also antagonizes the oxidative stress that arises by the action of these agents (Liu and Wang 2002; Wang et al. 2005).

The inhibition of melatonin biosynthesis in rats not only resulted in impairment of spatial memory but also induced an increase in tau phosphorylation, an effect prevented by melatonin supplementation (Zhu et al. 2004). Melatonin also prevented the oxidative damage and organelles injury found in animal models. The results point out to the involvement of decreased melatonin levels as a causative factor in the pathology of AD.

The oxidative stress is known to influence tau phosphorylation state (Gomez-Ramos et al. 2003; Lovell et al. 2004). The accumulation of misfolded and aggregated proteins in brain neurons of AD is considered a consequence of oxidative stress, in addition to the molecular structural changes due to age (Kenyon 2010). Since melatonin prevents, as an antioxidant and free radical scavenger, overproduction of free radicals, it seems feasible that the prevention of tau phosphorylation by melatonin is partly due to its antioxidant activity. In addition several studies indicated that melatonin may act as a modulator of enzymes in a way that is unrelated to its antioxidant properties. These include the regulation by melatonin of PKA (Schuster et al. 2005; Peschke et al. 2002), PKC (Witt-Enderby et al. 2000; Rivera-Bermudez et al. 2003), Ca2+/calmodulin-dependent kinase II (Benitez-King et al. 1996), and mitogen-activated protein kinase (Chan et al. 2002).

A major and early event in the pathogenesis of AD is the deficit in cholinergic function (Struble et al. 1982). Neurons in the nucleus basalis of Meynert, the major source of cholinergic innervation to the cerebral cortex and the hippocampus, undergo a profound and selective degeneration in AD brains (Samuel et al. 1994). The levels of acetylcholine (ACh) are reduced at the early stage of AD, whereas the activities of the synthesizing enzyme choline acetyltransferase (ChAT) and of the degradating enzyme acetylcholinesterase (AChE) do not change until a late phase of AD (Terry and Buccafusco 2003; Rinne et al. 2003). Since a profound decrease in ChAT activity in the neocortex of AD patients correlated with the severity of
dementia, the use of AChE inhibitors as a standard treatment of mild to moderate AD is now widely employed (Spencer et al. 2010).

Melatonin has a protective effect on the cholinergic system. It prevents the peroxynitrite-induced inhibition of choline transport and ChAT activity in synaptosomes and synaptic vesicles (Guermonprez et al. 2001). Melatonin treatment of 8-month-old APP695 transgenic mice significantly improved the profound reduction in ChAT activity in the frontal cortex and the hippocampus (Feng et al. 2004a). Melatonin also antagonizes the spatial memory deficit and the decreased ChAT activity found in adult ovariectomized rats (Feng et al. 2004b). However, in rats perfused intracerebroventricularly with Aβ for 14 days, melatonin was unable to restore the activity of ChAT (Tang et al. 2002). Melatonin inhibited lipopolysaccharide- and streptozotocin-induced increase in AChE activity (Agrawal et al. 2009). Recently hybrids of the AChE inhibitor tacrine and melatonin were synthesized as new drug candidates for treating AD (Fernandez-Bachiller et al. 2009; Spuch et al. 2010). These hybrids showed better antioxidant- and cholinergic-preserving activity tacrine or melatonin alone. The direct intracerebral administration of one of these hybrids decreased induced cell death and Aβ load in the APP/PS1 mouse brain parenchyma accompanied by a recovery of cognitive function (Spuch et al. 2010).

Another common factor in the pathogenesis of AD is the activation of microglia with consequent more expression of proinflammatory cytokines (Arends et al. 2000; Combadiere et al. 2007; Streit et al. 2004; Shen et al. 2007). Epidemiological studies have shown that the use of anti-inflammatory drugs decreases the incidence of AD (Stuchbury and Munch 2005). Aβ-induced microglial activation is a major source of inflammatory response (Park et al. 2012). Melatonin attenuated the production of proinflammatory cytokines induced by Aβ, NF kB, and nitric oxide in the rat brain (Rosales-Corral et al. 2003; Lau et al. 2012). Moreover, the DNA-binding activity of NF kB was inhibited by melatonin (Mohan et al. 1995; Chuang et al. 1996).

9.4 Clinical Aspects of Melatonin Application in AD

Normal aging is characterized by a decline of cognitive capacities including reasoning, memory, and semantic fluency, which is detectable as early as the fifth decade of life (Singh-Manoux et al. 2014). Although there is a high variability across cognitive domains measured and among individuals in the degree and timing of age-related cognitive losses, there is evidence for a preclinical stage in dementia in which cognitive performance is borderline as compared to normal aging (Silveri et al. 2007). In community-based studies, up to 28% of a sample of healthy community-dwelling elder shows deficits in performance that were not explained by age-related changes, education levels, mood, or health status. This strongly suggests the existence of early pathological changes which is a transitional state taking place between normal aging and early AD (Grundman et al. 2004).
Cross-sectional studies reveal that sleep disturbances are associated with memory and cognitive impairment (Fotuhi et al. 2009; Beaulieu-Bonneau and Hudon 2009; Cochen et al. 2009; Vecchierini 2010). A severe disruption of the circadian timing system occurs in AD as indicated by alterations in numerous overt rhythms like body temperature, glucocorticoids, and/or plasma melatonin (Weldemichael and Grossberg 2010; Harper et al. 2001; Mishima et al. 1999). The internal desynchronization of rhythms is significant in AD patients (Van Someren 2000). One emerging symptom is “sundowning,” a chronobiological phenomenon observed in AD patients in conjunction with sleep–wake disturbances. Sundowning includes symptoms like disorganized thinking, reduced ability to maintain attention to external stimuli, agitation, wandering, and perceptual and emotional disturbances, all appearing in late afternoon or early evening (Weldemichael and Grossberg 2010; Klaffke and Staedt 2006; Pandi-Perumal et al. 2002). Chronotherapeutic interventions such as exposure to bright light and/or timed administration of melatonin in selected circadian phases alleviated sundowning symptoms and improved sleep–wake patterns of AD patients (der Lek et al. 2008).

A number of studies have revealed that melatonin levels are lower in AD patients as compared to age-matched control subjects (Mishima et al. 1999; Skene et al. 1990; Ohashi et al. 1999; Liu et al. 1999). The decreased CSF melatonin levels of AD patients were attributed to a decreased melatonin production. CSF melatonin levels decreased even in preclinical stages (Braak stages-1) when patients did not manifest cognitive impairment (Zhou et al. 2003) suggesting thereby that reduction in CSF melatonin may be an early marker (and cause) for incoming AD. The decrease of melatonin levels in AD was attributed to a defective retinohypothalamic tract or SCN-pineal connections (Skene and Swaab 2003). Decreased MT₂ immunoreactivity and increased MT₁ immunoreactivity have been reported in the hippocampus of AD patients (Savaskan et al. 2002, 2005). Additionally β₁-adrenergic receptor mRNA levels decreased and the expression and activity of monoamine oxidase gene augmented in the pineal gland of AD patients (Wu et al. 2003).

The impaired melatonin production at night correlates significantly with the severity of mental impairment in demented patients (Magri et al. 1997). As AD patients have profound deficiency of endogenous melatonin, replacement of levels of melatonin in the brain could be a therapeutic strategy for arresting the progress of the disease. Melatonin’s neuroprotective and vasoprotective properties would help in improving the clinical condition of AD patients (Srinivasan et al. 2006).

There is published information indicating that melatonin, as a chronobiotic agent, is effective in treating irregular sleep–wake cycles and sundowning symptoms in AD patients (Fainstein et al. 1997; Jean-Louis et al. 1998a; Mishima et al. 2000; Cohen-Mansfield et al. 2000; Mahlberg et al. 2004; Brusco et al. 1998a; Cardinali et al. 2002; Asayama et al. 2003; Singer et al. 2003; Pappolla et al. 2000) (Table 9.1). In an initial study on 14 AD patients with 6–9 mg of melatonin given for a 2–3-year period, it was noted that melatonin improved sleep quality (Brusco et al. 1998a). Sundowning, diagnosed clinically, was no longer detectable in 12 out of 14 patients. Reduction in cognitive impairment and amnesia was also noted. This should be contrasted with the significant deterioration of the clinical conditions expected from patients after 1–3 year of evolution of AD.
Table 9.1 Studies including treatment of AD patients with melatonin

| Subjects                          | Design                           | Study’s duration | Treatment                        | Measured                                | Results                                                                 | Reference(s)                       |
|----------------------------------|----------------------------------|------------------|----------------------------------|-----------------------------------------|------------------------------------------------------------------------|------------------------------------|
| 10 demented patients             | Open-label study                 | 3 weeks          | 3 mg melatonin p.o./daily at bedtime | Daily logs of sleep and wake quality completed by caretakers | 7 out of 10 dementia patients having sleep disorders treated with melatonin showed a significant decrease in sundowning and reduced variability of sleep onset time | Fainstein et al. (1997)            |
| 14 AD patients                   | Open-label study                 | 22–35 months     | 9 mg melatonin p.o./daily at bedtime | Daily logs of sleep and wake quality completed by caretakers. Neuropsychological assessment | Sundowning was not longer detectable in 12 patients and persisted, although attenuated in 2 patients. A significant improvement of sleep quality was found. Lack of progression of the cognitive and behavioral signs of the disease during the time they received melatonin | Brusco et al. (1998a)              |
| Monozygotic twins with AD of 8 years duration | Case report | 36 months | One of the patients was treated with melatonin 9 mg p.o./daily at bedtime | Neuropsychological assessment Neuroimaging | Sleep and cognitive function severely impaired in the twin not receiving melatonin as compared to the melatonin-treated twin | Brusco et al. (1998b)              |
| 11 AD patients                   | Open-label study                 | 3 weeks          | 3 mg melatonin p.o./daily at bedtime | Daily logs of sleep and wake quality completed by the nurses | Significant decrease in agitated behaviors in all three shifts; significant decrease in daytime sleepiness | Cohen-Mansfield et al. (2000)      |
| 14 AD patients                   | Open-label, placebo-controlled trial | 4 weeks          | 6 mg melatonin p.o./daily at bedtime or placebo | Daily logs of sleep and wake quality completed by caretakers. Actigraphy | AD patients receiving melatonin showed a significantly reduced percentage of nighttime activity compared to a placebo group | Mishima et al. (2000)              |

(continued)
| Subjects   | Design                                      | Study’s duration | Treatment                                                                 | Measured                              | Results                                                                                     | Reference(s)              |
|-----------|---------------------------------------------|------------------|---------------------------------------------------------------------------|---------------------------------------|---------------------------------------------------------------------------------------------|---------------------------|
| 25 AD patients | Randomized double-blind placebo-controlled crossover study | 7 weeks          | 6 mg of slow-release melatonin p.o. or placebo at bedtime                  | Actigraphy                            | Melatonin had no effect on median total time asleep, number of awakenings, or sleep efficiency | Serfaty et al. (2002)     |
| 45 AD patients | Open-label study                           | 4 months         | 6–9 mg melatonin p.o./ daily at bedtime                                  | Daily logs of sleep and wake quality completed by caretakers. Neuropsychological assessment | Melatonin improved sleep and suppressed sundowning, an effect seen regardless of the concomitant medication employed | Cardinali et al. (2002)  |
| 157 AD patients | Randomized, placebo-controlled clinical trial | 2 months         | 2.5-mg slow-release melatonin, or 10-mg melatonin, or placebo at bedtime   | Actigraphy. Caregiver ratings of sleep quality | Nonsignificant trends for increased nocturnal total sleep time and decreased wake after sleep onset were observed in the melatonin groups relative to placebo. On subjective measures, caregiver ratings of sleep quality showed a significant improvement in the 2.5-mg sustained-release melatonin group relative to placebo | Singer et al. (2003)    |
| 20 AD patients  | Double-blind, placebo-controlled study      | 4 weeks          | Placebo or 3 mg melatonin p.o./ daily at bedtime                          | Actigraphy, Neuropsychological assessment | Melatonin significantly prolonged the sleep time and decreased activity in the night. Cognitive function was improved by melatonin               | Asayama et al. (2003)    |
| 7 AD patients   | Open-label study                           | 3 weeks          | 3 mg melatonin p.o./daily at bedtime                                     | Actigraphy, Neuropsychological assessment | Complete remission of day-night rhythm disturbances or sundowning was seen in 4 patients, with partial remission in other 2 | Mahlberg et al. (2004)   |

Table 9.1 (continued)
| 17 AD patients | Randomized, placebo-controlled study | 2 weeks | 3 mg melatonin p.o./daily at bedtime (7 patients). Placebo (10 patients) | Actigraphy. Neuropsychological assessment | In melatonin-treated group, actigraphic nocturnal activity and agitation showed significant reductions compared to baseline | Mahlberg and Walther (2007) |
|----------------|--------------------------------------|---------|-------------------------------------------------------------------------|---------------------------------------------|---------------------------------------------------------------------------------|-----------------------------|
| 68-year-old man with AD who developed rapid eye movement (REM) sleep behavior disorder | Case report | 20 months | 5–10 mg melatonin p.o./daily at bedtime | Polysomnography | Melatonin was effective to suppress REM sleep behavior disorder | Anderson et al. (2008) |
| 50 AD patients | Randomized, placebo-controlled study | 10 weeks | Morning light exposure (2,500 lx, 1 h) and 5 mg melatonin (n=16) or placebo (n=17) in the evening. Controls (n=17) received usual indoor light | Nighttime sleep variables, day sleep time, day activity, day/night sleep ratio, and rest–activity parameters were determined using actigraphy | Light treatment alone did not improve nighttime sleep, daytime wake, or rest-activity rhythm. Light treatment plus melatonin increased daytime wake time and activity levels and strengthened the rest-activity rhythm | Dowling et al. (2008) |
| 41 AD patients | Randomized, placebo-controlled study | 10 days | Melatonin (8.5 mg immediate release and 1.5 mg sustained release) (N=24) or placebo (N=17) administered at 10:00 P.M | Actigraphy | There were no significant effects of melatonin, compared with placebo, on sleep, circadian rhythms, or agitation | Gehrman et al. (2009) |
The administration of melatonin (6 mg/day) for 4 weeks to AD patients reduced nighttime activity as compared to placebo (Mishima et al. 2000). An improvement of sleep and alleviation of sundowning were reported in 11 AD patients treated with melatonin (3 mg/day at bedtime) and evaluated by using actigraphy (Mahlberg et al. 2004). Improvement in behavioral signs was reported with the use of 6–9 mg/day of melatonin for 4 months in AD patients with sleep disturbances (Cardinali et al. 2002).

In a double-blind study conducted on AD patients, it was noted that 3 mg/day of melatonin significantly prolonged actigraphically evaluated sleep time, decreased activity in night, and improved cognitive functions (Asayama et al. 2003). In a multicenter, randomized, placebo-controlled clinical trial of a sample of 157 AD patients with sleep disturbances, melatonin or placebo was administered for a period of 2 months (Singer et al. 2003). In actigraphic studies a trend to increased nocturnal total sleep time and decreased wake after sleep onset was noted in the melatonin-treated group. On subjective measures by caregiver ratings, significant improvement in sleep quality was noted with 2.5 mg sustained-release melatonin relative to placebo (Singer et al. 2003).

Negative results with the use of melatonin in fully developed AD were also published. For example, in a study in which melatonin (8.5 mg fast release and 1.5 mg sustained release) was administered at 10:00 PM for ten consecutive nights to patients with AD, no significant difference was noticed with placebo on sleep, circadian rhythms, and agitation (Gehrman et al. 2009). Although the lack of beneficial effect of melatonin in this study on sleep could be attributed to the short period of time examined, it must be noted that large interindividual differences among patients suffering from a neurodegenerative diseases are not uncommon. It should be also taken into account that melatonin, though having some sedating and sleep latency-reducing properties, does not primarily act as a sleeping pill, but mainly as a chronobiotic.

A review of the published results concerning melatonin use in AD (Cardinali et al. 2010) yielded eight reports (five open-label studies, two case reports) (N=89 patients) supporting a possible efficacy of melatonin: sleep quality improved and in patients with AD sundowning was reduced and cognitive decay slowed progression. In six double-blind, randomized placebo-controlled trials, a total number of 210 AD patients were examined. Sleep quality increased, sundowning decreased significantly, and cognitive performance improved in four studies (N=143), whereas there was absence of effects in two studies (N=67) (Cardinali et al. 2010).

Another systematic search of studies published between 1985 and April 2009 on melatonin and sundowning in AD patients was published (de Jonghe et al. 2010). All papers on melatonin treatment in dementia were retrieved, and the effects of melatonin on circadian rhythm disturbances were scored by means of scoring sundowning/agitated behavior, sleep quality, and daytime functioning. A total of nine papers, including four randomized controlled trials (n=243) and five case series (n=87), were reviewed. Two of the randomized controlled trials found a significant improvement in sundowning/agitated behavior. All five case series found an improvement. The results on sleep quality and daytime functioning were inconclusive (de Jonghe et al. 2010).
Therefore, whether melatonin has any value in preventing or treating AD remains uncertain. It must be noted that one of the problems with AD patients with fully developed pathology is the heterogeneity of the group examined. Moreover, the reduced hippocampal expression of MT$_2$ melatonin receptors in AD patients (Savaskan et al. 2005) and of MT$_1$ receptors in the circadian apparatus at later stages of the disease may explain why melatonin treatment is less effective or erratic at this stage (Wu et al. 2007).

Mild cognitive impairment (MCI) is diagnosed in those who have an objective and measurable deficit in cognitive functions, but with a preservation of daily activities. The estimates of annual conversion rates to dementia vary across studies but may be as high 10–15% (Farias et al. 2009), MCI representing a clinically important stage for identifying and treating individuals at risk. Indeed, the degenerative process in AD brain starts 20–30 years before the clinical onset of the disease (Davies et al. 1988; Price and Morris 1999). During this phase, plaques and tangle loads increase and at a certain threshold the first symptom appears (Braak and Braak 1995, 1998).

CSF melatonin levels decrease even in preclinical stages of AD when the patients do not manifest any cognitive impairment, suggesting that the reduction in CSF melatonin may be an early trigger and marker for AD (Zhou et al. 2003; Wu et al. 2003). Although it is not known whether the relative melatonin deficiency is either a consequence or a cause of neurodegeneration, it seems clear that the loss in melatonin aggravates the disease and that early circadian disruption can be an important deficit to be considered.

We previously reported a retrospective analysis in which daily 3–9 mg of a fast-release melatonin preparation p.o. at bedtime for up to 3 years significantly improved cognitive and emotional performance and daily sleep–wake cycle in 25 MCI patients (Furio et al. 2007). Recently we reported data from another series of 96 MCI outpatients, 61 of whom had received daily 3–24 mg of a fast-release melatonin preparation p.o. at bedtime for 15–60 months in comparison to a similar group of 35 MCI patients who did not receive it (Cardinali et al. 2012a). In addition, all patients received the individual standard medication considered appropriate by the attending psychiatrist.

Patients treated with melatonin exhibited significantly better performance in mini–mental state examination and the cognitive subscale of the AD Assessment Scale. After application of a neuropsychological battery comprising a Mattis’ test, digit–symbol test, Trail A and B tasks, and the Rey’s verbal test, better performance was found in melatonin-treated patients for every parameter tested (Cardinali et al. 2012a). Abnormally high Beck Depression Inventory scores decreased in melatonin-treated patients, concomitantly with the improvement in the quality of sleep and wakefulness. These results further support that melatonin is a useful add-on drug for treating MCI in a clinic environment.

Thus, an early initiation of treatment can be decisive for therapeutic success (Quinn et al. 2005). In Table 9.2, published data concerning melatonin treatment in MCI are summarized. Six double-blind, randomized placebo-controlled trials and two open-label retrospective studies (N=782) consistently showed that the
Table 9.2  Studies including treatment of MCI patients with melatonin

| Subjects | Design                                      | Study’s duration | Treatment                                      | Measured                                         | Results                                                                 | Reference(s)                                                                 |
|----------|---------------------------------------------|------------------|------------------------------------------------|------------------------------------------------|-------------------------------------------------------------------------|----------------------------------------------------------------------------|
| 10 patients with MCI | Double-blind, placebo-controlled, crossover study | 10 days          | 6 mg melatonin p.o./ daily at bedtime          | Actigraphy. Neuropsychological assessment      | Melatonin enhanced the rest-activity rhythm and improved sleep quality. Total sleep time unaffected. The ability to remember previously learned items improved along with a significant reduction in depressed mood | Jean-Louis et al. (1998b)                                                  |
| 26 individuals with age-related MCI | Double-blind, placebo-controlled pilot study             | 4 weeks          | 1 mg melatonin p.o. or placebo at bedtime      | Sleep questionnaire and a battery of cognitive tests at baseline and at 4 weeks | Melatonin administration improved reported morning “restedness” and sleep latency after nocturnal awakening. It also improved scores on the California Verbal Learning Test-interference subtest | Peck et al. (2004)                                                        |
| 354 individuals with age-related MCI | Randomized, double-blind, placebo-controlled study       | 3 weeks          | Prolonged-release melatonin (Circadin, 2 mg) or placebo, 2 h before bedtime | Leeds Sleep Evaluation and Pittsburgh Sleep Questionnaires, and Clinical Global Improvement scale score and quality of life | PR-melatonin resulted in significant and clinically meaningful improvements in sleep quality, morning alertness, sleep onset latency, and quality of life | Wade et al. (2007)                                                       |
| 60 MCI outpatients | Open-label, retrospective study                | 9–24 months      | 35 patients received daily 3–9 mg of a fast-release melatonin preparation p.o. at bedtime. Melatonin was given in addition to the standard medication | Daily logs of sleep and wake quality. Initial and final neuropsychological assessment | Abnormally high Beck Depression Inventory scores decreased in melatonin-treated patients, concomitantly with an improvement in wakefulness and sleep quality. Patients treated with melatonin showed significantly better performance in neuropsychological assessment | Cardinali et al. (2010) and Furio et al. (2007) |
| Study Design | Intervention | Duration | Outcomes | Comments |
|--------------|--------------|----------|----------|----------|
| 189 individuals with age-related cognitive decay | Long-term, double-blind, placebo-controlled, 2 × 2 factorial randomized study | 1–3.5 years | Long-term daily treatment with whole-day bright (1,000 lx) or dim (300 lx) light. Evening melatonin (2.5 mg) or placebo administration | Standardized scales for cognitive and noncognitive symptoms, limitations of activities of daily living, and adverse effects assessed every 6 months | Light-attenuated cognitive deterioration and ameliorated depressive symptoms. Melatonin-shorted sleep onset latency and increased sleep duration but adversely affected scores for depression. The combined treatment of bright light plus melatonin showed the best effects |
| 22 individuals with age-related cognitive decay | Prospective, randomized, double-blind, placebo-controlled, study | 2 months | Participants received 2 months of melatonin (5 mg p.o. /day) and 2 months of placebo | Sleep disorders were evaluated with the Northside Hospital Sleep Medicine Institute (NHSMI) test. Behavioral disorders were evaluated with the Yesavage Geriatric Depression Scale and Goldberg Anxiety Scale | Melatonin treatment significantly improved sleep quality scores. Depression also improved significantly after melatonin administration |
| 25 MCI outpatients | Randomized, double-blind, placebo-controlled study | 12 weeks | 11 patients received an oily emulsion of docosahexaenoic acid phospholipids containing melatonin (10 mg) and tryptophan (190 mg) | Neuropsychological assessment of orientation and cognitive functions, short-term and long-term memory, attentional abilities, executive functions, visuconstructional and visuospatial abilities, language, and mood | Older adults with MCI had significant improvements in several measures of cognitive function when supplemented with an oily emulsion of DHA-phospholipids containing melatonin and tryptophan for 12 weeks, compared with the placebo. The antioxidant capacity of erythrocytes and membrane lipid composition improved after treatment |

(continued)
| Subjects                  | Design                                | Study’s duration | Treatment                                                                 | Measured                                                                 | Results                                                                                                                                                                                                 | Reference(s)               |
|--------------------------|---------------------------------------|------------------|---------------------------------------------------------------------------|---------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------|
| 96 MCI outpatients       | Open-label, retrospective study       | 15–60 months     | 61 patients received daily 3–24 mg of a fast-release melatonin preparation p.o. at bedtime. Melatonin was given in addition to the standard medication | Daily logs of sleep and wake quality. Initial and final neuropsychological assessment | Abnormally high Beck Depression Inventory scores decreased in melatonin-treated patients, concomitantly with an improvement in wakefulness and sleep quality. Patients treated with melatonin showed significantly better performance in neuropsychological assessment. Only 6 out of 61 patients treated with melatonin needed concomitant benzodiazepine treatment vs. 22 out of 35 MCI patients not receiving melatonin | Cardinali et al. (2012a)   |
administration of daily evening melatonin improves sleep quality and cognitive performance in MCI patients. Therefore, melatonin treatment could be effective at early stages of the neurodegenerative disease.

There are two reasons why the use of melatonin is convenient in MCI patients. In the course of the neurodegenerative process, the age-related deterioration in circadian organization becomes significantly exacerbated and is responsible of behavioral problems like sundowning (Wu and Swaab 2007). Age-related cognitive decline in healthy older adults can be predicted by the fragmentation of the circadian rhythm in locomotor behavior. Hence, replacement of the low melatonin levels occurring in the brain (Zhou et al. 2003; Wu et al. 2003) can be highly convenient in MCI patients. On the other hand, the bulk of information on the neuroprotective properties of melatonin derived from experimental studies (see for ref. (Pandi-Perumal et al. 2013; Rosales-Corral et al. 2012)) turns highly desirable to employ pharmacological doses in MCI patients with the aim of arresting or slowing disease’s progression.

The sleep-promoting activity of melatonin in humans has been known for years (Vollrath et al. 1981; Waldhauser et al. 1990), and a number of studies pointed to a beneficial effect of melatonin in a wide variety of sleep disorders (see for ref. (Cardinali et al. 2012b)). However, controversy continues to surround claims of melatonin’s therapeutic potential. A meta-analysis on the effects of melatonin in sleep disturbances at all age groups (including young adults with presumably normal melatonin levels) failed to document significant and clinically meaningful effects of exogenous melatonin on sleep quality, efficiency, and latency (Buscemi et al. 2006). However, another meta-analysis involving 17 controlled studies in old subjects has shown that melatonin was effective in increasing sleep efficiency and in reducing sleep onset latency (Brzezinski et al. 2005). After the approval by the European Medicines Agency of a prolonged-release form of 2 mg melatonin (Circadin®, Neurim, Tel Aviv, Israel) for treatment of insomnia in patients ≥55 years of age, a recent consensus of the British Association for Psychopharmacology on evidence-based treatment of insomnia, parasomnia, and circadian rhythm sleep disorders concluded that prolonged-release melatonin is the first-choice treatment when a hypnotic is indicated in old patients (Wilson et al. 2010).

In addition to sleep promotion, melatonin has a mild sedating effect. This may be the cause for the decrease in Beck’s score seen in MCI studies. Melatonin has a facilitatory effect on GABAergic transmission (Cardinali et al. 2008) which may be responsible for the anticonvulsant, anxiolytic, antihyperalgesic, and antinociceptive effects of the methoxyindole.

The mechanisms accounting for the therapeutic effect of melatonin in MCI patients remain to be defined. Melatonin treatment mainly promotes slow-wave sleep in the elderly (Monti et al. 1999) and can be beneficial in MCI by augmenting the restorative phases of sleep, including the augmented secretion of GH and neurotrophins. As outlined above, melatonin acts at different levels relevant to the development and manifestation of AD. The antioxidant, mitochondrial, and anti-amyloidogenic effects can be seen as a possibility of interfering with the onset of the disease. Therefore, to start melatonin treatment as soon as possible can be decisive for the final response (Quinn et al. 2005).
One important aspect to be considered is the melatonin dose employed, which may be unnecessarily low when one takes into consideration the binding affinities, half-life, and relative potencies of the different melatonin agonists on the market. In addition to being generally more potent than the native molecule, melatonin analogs are employed in considerably higher amounts (Cardinali et al. 2011a). Licensed doses of the melatonin receptor agonist ramelteon vary from 8 to 32 mg/day while agomelatine has been licensed for treatment of major depressive disorder at doses of 25–50 mg/day. In clinical studies involving healthy human subjects, tasimelteon, another melatonin receptor agonist (Vanda Pharmaceuticals, Washington, DC, USA), was administered at doses of 10–100 mg/day (Rajaratnam et al. 2009), while pharmacokinetics, pharmacodynamics, and safety of the melatonin receptor agonist TIK-301 (Tikvah Pharmaceuticals, Atlanta, GA, USA) have been examined in a placebo-controlled study using 20–100 mg/day (Mulchahey et al. 2004). Therefore, studies in MCI with melatonin doses in the range of 75–100 mg/day are further warranted.

Indeed, melatonin has a high safety profile; it is usually remarkably well tolerated and, in some studies, it has been administered to patients at very large doses. Melatonin (300 mg/day) for up to 3 years decreased oxidative stress in patients with amyotrophic lateral sclerosis (Weishaupt et al. 2006). In children with muscular dystrophy, 70 mg/day of melatonin reduced cytokines and lipid peroxidation (Chahbouni et al. 2010). Doses of 80 mg melatonin hourly for 4 h were given to healthy men with no undesirable effects other than drowsiness (Waldhauser et al. 1984). In healthy women given 300 mg melatonin/day for 4 months, there were no side effects (Voordouw et al. 1992). A recent randomized controlled double-blind clinical trial on 50 patients referred for liver surgery indicated that a single preoperative enteral dose of 50 mg/kg melatonin (i.e., an equivalent to 3 g for a 60-kg adult) was safe and well tolerated (Nickkhelgh et al. 2011).

Another outcome of the study reported in (Cardinali et al. 2012a) was that when melatonin is employed much less benzodiazepines are needed to treat sleep disturbances in MCI. Since, as above mentioned, melatonin and benzodiazepines shared some neurochemical (i.e., interaction with GABA-mediated mechanisms in the brain (Cardinali et al. 2008)) and behavioral properties (e.g., a similar day-dependent anxiolytic activity (Golombek et al. 1996)), melatonin therapy was postulated to be an effective tool to decrease the dose of benzodiazepines needed in patients (Fainstein et al. 1997; Dagan et al. 1997; Garfinkel et al. 1999; Siegrist et al. 2001). A recent retrospective analysis of a German prescription database identified 512 patients who had initiated treatment with prolonged-release melatonin (2 mg) over a 10-month period (Kunz et al. 2012). From 112 patients in this group who had previously used benzodiazepines, 31% discontinued treatment with benzodiazepines 3 months after beginning prolonged-release melatonin treatment. The discontinuation rate was higher in patients receiving two or three melatonin prescription (Kunz et al. 2012). The prolonged use of benzodiazepines and benzodiazepine receptor agonists (Z-drugs) is related to severe withdrawal symptoms and potential dependency which has become a public health issue leading to multiple campaigns to decreases consumption of these drugs. A recent pharmacoepidemiological study concluded that these campaigns generally failed when they were not associated with the availability and market of melatonin (Clay et al. 2013).
In conclusion, the question as to whether melatonin has a therapeutic value in preventing or treating MCI, affecting disease initiation or progression of the neuropathology and the driving mechanisms, deserved further analysis in future studies. Double-blind multicenter studies are needed to further explore and investigate the potential and usefulness of melatonin as an antidementia drug at the early stage of disease.

9.5 Basic Aspects of Melatonin Activity in Animal Models of PD

PD is a major neurodegenerative disease characterized, in its clinically relevant stages, by the progressive degeneration of dopamine (DA)-containing neurons in the substantia nigra (Rothman and Mattson 2012; Seppi et al. 2011). Typical of PD are cellular inclusions called Lewy bodies. They are single or multiple intraneuronal inclusions selectively distributed in the cytoplasm and having various sizes and shapes depending on the brain area that is affected. Lewy bodies have a relatively restricted distribution and are usually associated with DA neurons of the substantia nigra pars compacta (SNpc) and ventral tegmental region, noradrenergic neurons of the locus coeruleus, catecholamine cells of the medulla oblongata, serotonergic neurons of the raphe nuclei, and specific cholinergic neurons (Rothman and Mattson 2012; Seppi et al. 2011).

Several studies indicate that accumulation of fibrillar α-synuclein aggregates is associated with PD and other Lewy body diseases (Fornai et al. 2005). Mitochondrial dysfunction plays a role in this process. Protein misfolding and aggregation in vivo can be suppressed or promoted by several factors, among them free radicals. It has thus been postulated that aggregation of α-synuclein might be one of many possible links that connect mitochondrial dysfunction to neurodegeneration (Fornai et al. 2005).

Animal models of altered brain DA function have been developed by injecting 6-hydroxydopamine (6-OHDA) into the nigrostriatal pathway of the rat or by injecting the neurotoxin 1-methyl-4-phenyl-1,2,3,6 tetrahydropyridine (MPTP). MPTP-induced parkinsonism in animals is preferred over the other neurotoxin-induced models due to its potential to cause the disease in humans and in subhuman primates. MPTP is selective to the neurons in SNpc region and causes severe loss of striatal spines in nonhuman primates (Herraiz and Guillen 2011), a consistent neuropathologic phenomenon observed in postmortem PD brains.

MPTP administered to rats is selectively taken up by astrocytes and is metabolized into methyl 1-4 phenyl pyridinium (MPP⁺). This cation is selectively taken up by dopaminergic neurons and causes increased production of free radicals, depletion of ATP, and apoptosis. In the case of 6-OHDA, the neurotoxin selectively destroys nigrostriatal neurons by causing enhanced release of free radicals. It should be stressed, however, that these animal models do not reflect the prodromal early changes in upper spinal cord and brain stem seen in PD and therefore are presumably meaningless in terms of etiology.

With some exceptions the role of melatonin in prevention and treatment of experimental PD is now supported by experimental data. Acuña-Castroviejo et al.
used an MPTP model to show that melatonin could counteract MPTP-induced lipid peroxidation in striatum, hippocampal, and midbrain regions (Acuña-Castroviejo et al. 1997). Using the 6-OHDA model, Mayo et al. showed that when added to incubation medium containing 6-OHDA, melatonin significantly prevented the increased lipid peroxidation which normally would have occurred in cultured PC 12 cells (Mayo et al. 1998). Melatonin also increased the levels of antioxidant enzymes (Mayo et al. 1998). Additionally, melatonin reduced pyramidal cell loss in the hippocampus, a cellular area which undergoes degeneration in the brains of PD patients and which presumably causes memory deficits in affected patients. Thomas and Mohanakumar similarly demonstrated in vitro and ex vivo models, as well as in an in vivo MPTP rodent model, that melatonin had potent hydroxyl radical scavenger activity in the mouse striatum and in isolated mitochondria (Thomas and Mohanakumar 2004). In addition to these primary effects, the investigators also found secondary increases in SOD activity.

The attenuation of MPTP-induced superoxide formation indicates an additional neuroprotective mechanism by melatonin. Intra-median forebrain bundle infusion of a ferrous-ascorbate-DA hydroxyl radical (•OH) generating system, which causes significant depletion of striatal DA, could be significantly attenuated by melatonin administration (Borah and Mohanakumar 2009). In another study, Antolín et al. used the MPTP model and found that melatonin was effective in preventing neuronal cell death in the nigrostriatal pathway as indicated by the number of preserved DA cells, of tyrosine hydroxylase levels, and other ultrastructural features (Antolín et al. 2002). The findings thus demonstrated that melatonin clearly prevents nigral dopaminergic cell death induced by chronic treatment with MPTP.

α-Synuclein assembly is a critical step in the development of Lewy body diseases such as PD and dementia with Lewy bodies. Melatonin attenuated kainic acid-induced neurotoxicity (Chang et al. 2012) and arsenite-induced apoptosis (Lin et al. 2007) via inhibition of α-synuclein aggregation. Melatonin also decreased the expression of α-synuclein in dopamine-containing neuronal regions after amphetamine both in vivo (Sae-Ung et al. 2012) and in vitro (Klongpanichapak et al. 2008).

In another study melatonin effectively blocked α-synuclein fibril formation and destabilized preformed fibrils. It also inhibited protofibril formation, oligomerization, and secondary structure transitions of α-synuclein as well as reduced α-synuclein cytotoxicity (Chang et al. 2012; Brito-Armas et al. 2013).

MPTP elicits its neurotoxic effects by increasing the amount of •NO derived from iNOS. This action mainly affects DA neurons while •NO derived from neuronal NOS (nNOS) has a damaging effect on dopaminergic fibers and terminals in the striatum. A future therapy for PD may require agents that inhibit the degenerative effects of iNOS in the substantia nigra pars compacta (Zhang et al. 2000). Since melatonin can effectively downregulate iNOS and prevent •NO formation in the brain (Cuzzocrea et al. 1997; Escames et al. 2004), it should be regarded as a drug of choice for arresting the neuronal degeneration associated with PD.

MPTP, through its metabolite MPP⁺, causes direct inhibition of Complex I of the mitochondrial electron transport chain. Such an inhibition of Complex I has been reported in the substantia nigra of patients suffering from PD. By increasing Complex I and IV activities of the mitochondrial electron transport chain, melatonin
exerts one of its antioxidant effects (Acuña-Castroviejo et al. 2011). Melatonin also stimulates the gene expression of three antioxidant enzymes Cu/Zn-SOD, Mn-SOD, and GPx in cultured dopaminergic cells (Mayo et al. 1998).

Symptomatically effective treatment for PD in modern medicine is by supplementation of DA in its precursor form that crosses the blood–brain barrier. However, long-term administration DA precursor typically leads to motor complications, such as 1-dihydroxyphenylalanine (1-DOPA)-induced dyskinesias (Carta et al. 2004; Wernke et al. 2006). It is also shown that administration of this drug in high doses leads to generation of neurotoxic molecules such as 6-OHDA. Therefore, efforts are in the vogue to reduce the intake or to compensate for the side effects of this drug. In a recent study undertaken to examine whether melatonin could potentiate the effect of a low dose of 1-DOPA in MPTP-induced experimental parkinsonism in mice, melatonin, but not 1-DOPA, restored spine density and spine morphology of medium spiny neurons in the striatum suggesting that melatonin could be an ideal adjuvant to 1-DOPA therapy in PD, making it possible to bring down the therapeutic doses of 1-DOPA (Naskar et al. 2013).

It has been proposed that an abnormal assembly of the cytoskeleton is involved in the pathogenesis of neurodegenerative diseases. Lewy bodies, which are considered to be cytopathologic markers of parkinsonism, comprise abnormal arrangements of tubulin, MAP 1 and MAP 2 (Beach et al. 2009). Melatonin is very effective in promoting cytoskeletal rearrangements and thus may have a potential therapeutic value in the treatment of neurodegenerative diseases including parkinsonism (Benitez-King et al. 2004).

It must be noted that other studies do not support the hypothesis that melatonin is of therapeutic benefit in parkinsonism. For instance, reduction of melatonin by pinealectomy, or by exposure of rats to bright light to inhibit melatonin synthesis, has been found to enhance recovery from parkinsonism, i.e., spontaneous remission of symptoms following 6-OHDA or MPTP have been observed, whereas melatonin administration aggravated them (Willis and Armstrong 1999; Tapias et al. 2010), using a rotenone model of PD in rats, found that melatonin administration led to striatal catecholamine depletion, striatal terminal loss, and nigral DA cell loss and thus was not neuroprotective. Indeed, the use of melatonin as an adjunct therapy to either halt progressive degeneration or for providing symptomatic relief in PD patients has been questioned (Willis and Robertson 2004).

### 9.6 Clinical Aspects of Melatonin Application in PD

Key symptoms of PD such as tremor, rigidity, bradykinesia, and postural instability develop when about three-fourth of dopaminergic cells are lost in the SNpc, and consequently the smooth, coordinated regulation of striatal motor circuits is hampered (Maguire-Zeiss and Federoff 2010; Tansey et al. 2007). However, PD does not start in the nigrostriatum, but rather in the brainstem or even the spinal cord of subjects who remain asymptomatic for a long period of time (Braak et al. 2003).
Other, non-motor symptoms are seen in PD, and some of them, such as hyposmia, depression, or rapid eye movement (REM)-associated sleep behavior disorder (RBD), can precede the onset of disease. Non-motor symptoms are often misdiagnosed and untreated, although their appearance is an index of a worse prognosis and lower quality of life. Indeed up to 65% of patients diagnosed with RBD, which is characterized by the occurrence of vivid, intense, and violent movements during REM sleep, subsequently developed PD within an average lag time of 12–13 years.

Administration of melatonin 3–12 mg at bedtime has been shown to be effective in the treatment of RBD (Kunz and Bes 1997, 1999; Takeuchi et al. 2001; Boeve et al. 2003; Anderson and Shnze 2009). A total of 119 patients have been reported (Table 9.3). For example, in a study reporting the records of 45 consecutive RBD patients seen at Mayo Clinic between 2008 and 2010, 25 patients receiving melatonin (6 mg daily) reported significantly reduced injuries and fewer adverse effects (McCarter et al. 2013).

Polysomnography showed statistically significant decreases in the number of R epochs without atonia and in the movement time in R. This contrasted with the persistence of tonic muscle tone in R sleep seen with patients treated with clonazepam. Because of these data a clinical consensus recommended melatonin use in RBD at Level B, i.e., “assessment supported by sparse high grade data or a substantial amount of low grade data and/or clinical consensus by the task force” (Aurora et al. 2010). In another consensus statement generated in 2011, a claim for eventual trials with disease-modifying and neuroprotective agents in RBD was urged based on the high conversion rate from idiopathic RBD to parkinsonian disorders (Schenck et al. 2013). Six inclusion criteria and 24 exclusion criteria were identified for symptomatic therapy and neuroprotective trials (Schenck et al. 2013).

At this time, there is no treatment that will delay or stop the progression of PD, and medications currently available are mostly symptomatic. The increasing incidence of age-associated neurodegenerative diseases has been attributed to the augmented generation of free radicals and the associated oxidative stress, which is enhanced in certain regions of the aging brain (Gibson et al. 2010; Olanow 1992; Fahn and Cohen 1992). Increased lipid peroxidation, decreased levels of GSH, and increased iron levels occur in the brains of patients suffering from parkinsonism (Dexter et al. 1989). As the increased iron levels can promote the Fenton reaction, it seems feasible that an increased hydroxyl radical formation induces free radical damage. Free radical damage of lipids, proteins, and nucleic acids has all been reported in the substantia nigra of parkinsonian patients (Alam et al. 1997). Oxidative stress has been suggested to be the major cause of dopaminergic neuronal cell death. Exposure to high concentrations of H2O2 that are formed during oxidation of DA by monoamine oxidase (MAO) may also be a major cause for destruction of dopaminergic neurons in parkinsonism (Fahn and Cohen 1992). Therefore, within this context the cytoprotective properties exhibited by melatonin are promising as a tool in PD prevention.

The study of melatonin secretion in PD has revealed some interesting findings. In related studies a phase advance in nocturnal melatonin levels in L-DOPA-treated parkinsonian patients was noted, but this was not observed in untreated patients when
| Subjects | Design | Study’s duration | Treatment | Measured | Results | Reference(s) |
|----------|--------|------------------|-----------|----------|---------|--------------|
| 40 PD patients | Open-label, placebo-controlled trial | 2 weeks | 5–50 mg melatonin p.o./daily at bedtime. All subjects were taking stable doses of antiparkinsonian medications | Actigraphy | Relative to placebo, treatment with 50 mg of melatonin significantly increased nighttime sleep, as revealed by actigraphy. As compared to 50 mg or placebo, administration of 5 mg of melatonin was associated with significant improvement of sleep in the subjective reports | Dowling et al. (2005) |
| 18 PD patients | Open-label, placebo-controlled trial | 4 weeks | 3 mg melatonin p.o./daily at bedtime | Polysomnography (PSG). Subjective evaluation by the Pittsburgh Sleep Quality Index and Epworth Sleepiness Scale | On initial assessment, 14 patients showed poor-quality sleep EDS. Increased sleep latency (50 %), REM sleep without atonia (66 %), and reduced sleep efficiency (72 %) were found in PSG. Melatonin significantly improved subjective quality of sleep. Motor dysfunction was not improved by the use of melatonin | Medeiros et al. (2007) |
| 38 patients with PD without dementia and with complaints on sleep disorders | Open-label trial | 6 weeks | Group 1 (n=20) received 3 mg melatonin in addition to the previous dopaminergic group 2 (n=18) received clonazepam 2 mg at night | Polysomnography (PSG) at baseline and at the end of the trial. Subjective evaluation by the PD sleep scale (PDSS) and the Epworth Sleepiness Scale (ESS). Neuropsychological testing using MMSE, five-word test, digit span, and the Hamilton scale | Compared to baseline, melatonin and clonazepam reduced sleep disorders in patients. The daytime sleepiness (ESS) was significantly increased in the clonazepam group. Patients treated with melatonin had better scores on the MMSE, five-word test, Hamilton scale at the end of the study period as compared with the clonazepam group. Changes in total point scores on the PSG at the end of week 6 were in favor of the group treated with melatonin | Litvinenko et al. (2012) |
| 1 RBD patient | Case report | 5 months | 3 mg melatonin p.o./daily at bedtime | Actigraphy, PSG | Significant reduction of motor activity during sleep, as measured by actigraphy. After 2 months’ treatment, PSG showed no major changes except an increase of REM sleep | Kunz and Bes (1997) |

(continued)
| Subjects              | Design                | Study’s duration | Treatment                                      | Measured | Results                                                                 | Reference(s)                  |
|----------------------|-----------------------|------------------|------------------------------------------------|----------|-------------------------------------------------------------------------|--------------------------------|
| 6 consecutive RBD patients | Open-label prospective case series | 6 weeks         | 3 mg melatonin p.o./daily at bedtime           | PSG      | Significant PSG improvement in 5 patients within a week which extended beyond the end of treatment for weeks or months | Kunz and Bes (1999)           |
| 14 RBD patients      | Open-label prospective case series | Variable        | 3–9 mg melatonin p.o./daily at bedtime         | PSG      | Thirteen patients and their partners noticed a suppressing effect on problem sleep behaviors after melatonin administration. % tonic REM activity in PSG findings was decreased after melatonin administration. Melatonin concentrations in 10 RBD patients were under 30 pg/mL at maximal values; their mean 33.5 pg/mL. RBD patients with low melatonin secretion tended to respond to melatonin therapy | Takeuchi et al. (2001)         |
| 14 RBD patients      | Retrospective case series | 14 months       | 3–12 mg melatonin p.o./daily at bedtime        | PSG      | 8 patients experienced continued benefit with melatonin beyond 12 months of therapy | Boeve et al. (2003)            |
| 39 RBD patients      | Retrospective case series | 27–53 months    | All initially treated with clonazepam. When melatonin was used, it was given at a 10 mg p.o./daily at bedtime | PSG      | 21 patients continued to take clonazepam, 8 used another medication, and 4 required a combination of medications to control symptoms adequately. Zopiclone was used in 11 patients either alone or in combination. Two patients used melatonin (10 mg) and both found it effective. Combination therapy (clonazepam/gabapentin/melatonin) was used in one patient | Anderson and Shneerson (2009)   |
| 25 RBD patients      | Retrospective case series | 27–53 months    | 6 mg melatonin p.o./daily at bedtime           |          | As compared to clonazepam-treated RBD patients (n=18), patients receiving melatonin reported significantly reduced injuries and fewer adverse effects | McCarter et al. (2013)         |
compared to control subjects (Fertl et al. 1993). Similar findings were noted in studies in which a phase advance of about 2 h in plasma melatonin secretion was seen in PD patients receiving dopaminergic treatment when compared to untreated patients (Bordet et al. 2003). This study also confirmed previous findings that L-DOPA treatment influenced melatonin secretion rhythmicity. An increase in daytime melatonin secretion was also noted in L-DOPA-treated patients. An increase in melatonin secretion may be one of the adaptive responses to neurodegeneration (Bordet et al. 2003) and could play a neuroprotective role through an antioxidant effect.

The occurrence of motor fluctuations in PD was related to fluctuations in serum melatonin levels, a finding that was attributed to interactions of monoamines with melatonin in the striatal complex (Escames et al. 1996). Melatonin may exert direct motor effects through its interactions with DA and serotonin. Changes in levodopa-related motor complications may be related to changes in melatonin secretion pattern. L-DOPA-related motor complications occur in nearly half of the patients with PD on completion of the first 5 years of treatment (Koller 1996), and as noted above, results on experimental parkinsonism in mice support the use of melatonin as an adjuvant to L- to bring down the therapeutic doses of L-DOPA in PD (Naskar et al. 2013).

The hypothesis that melatonin has an inhibitory motor effect which is probably involved in wearing-off episode (i.e., the progressively shorter intervals during which symptoms remain adequately controlled as if the effects of medication would start to “wear off”) has been supported by some therapeutic studies. Stimulation of globus pallidus inhibited an increase in daytime plasma melatonin levels in parkinsonian patients as compared to healthy subjects (Catala et al. 1997) and was also reported to improve motor symptoms and complications in patients with PD (Olanow et al. 2000). Melatonin may be useful in halting or retarding the progressive degeneration of PD and may hold further promise for inhibiting the L-DOPA-related motor complications.

Because of the lower rates of cancer mortality/incidence in patients with PD, speculations about risk or preventative factors common to both diseases, including lifestyle factors (such as smoking) and genetic susceptibility, have been entertained. Relevant to the subject of the present review is that preliminary epidemiological evidence suggests that longer years of working night shifts are associated with reduced melatonin levels and reduced risk of PD among, whereas longer hours of sleep appear to increase their risk (Schernhammer and Schulmeister 2004). While lower melatonin concentrations may predict a higher cancer risk, there is also some evidence that they may be associated with a lower risk of PD.

The finding that a reduced expression of melatonin MT₁ and MT₂ receptors occurs in amygdala and substantia nigra in patients with PD (Adi et al. 2010) indicates that there is a possibility that the melatonergic system is involved in the abnormal sleep mechanisms seen as well as in its overall pathophysiology. Melatonin has been used for treating sleep problems, insomnia, and daytime sleepiness in PD patients. In a study undertaken on 40 patients (11 women, 29 men; range 43–76 years) melatonin was administered for a treatment period of 2 weeks, in doses ranging from 5 mg to 50 mg/day (Dowling et al. 2005). To avoid the possibility of producing a circadian shift, melatonin was administered 30 min before bedtime (circadian
shifts can occur if administered melatonin is administered at any other time). All subjects were taking stable doses of antiparkinsonian medications during the course of the study. Relative to placebo, treatment with 50 mg of melatonin significantly increased nighttime sleep, as revealed by actigraphy. As compared to 50 mg or placebo, administration of 5 mg of melatonin was associated with significant improvement of sleep in the subjective reports. The study also found that the high dose of melatonin (50 mg) was well tolerated (Dowling et al. 2005).

In another study 18 PD patients were randomized after performing a basal polysomnography to receive melatonin (3 mg) or placebo 1 h before bedtime for 4 weeks (Medeiros et al. 2007). Subjective sleep quality was assessed by the Pittsburgh Sleep Quality Index and daytime somnolence by the Epworth Sleepiness Scale. All measures were repeated at the end of treatment. On initial assessment, 14 patients (70 %) showed poor-quality sleep and 8 (40 %) excessive diurnal somnolence. Increased sleep latency (50 %), REM sleep without atonia (66 %), and reduced sleep efficiency (72 %) were found in PSG. Sleep fragmentation tended to be more severe in patients on lower doses of L-DOPA, although melatonin significantly improved subjective quality of sleep. The objective abnormalities remained unchanged. Motor dysfunction was not improved by the use of melatonin (Medeiros et al. 2007).

Exposure to light of 1,000–1,500 lx intensity for 1–1.5 h, 1 h prior to bedtime for 2–5 weeks, has been found to improve the bradykinesia and rigidity observed in 12 PD patients (Willis and Turner 2007). A reduction in agitation and psychiatric side effects was also reported in this study. The authors suggested that activation of the circadian system by antagonizing melatonin secretion with bright light has a therapeutic value for treating the symptoms of PD (Willis 2008).

However, bright light has been employed in a number of studies for treating depressive symptoms, and the view has been advanced that suppression of melatonin secretion is not the likely mechanism by which artificial light exerts its therapeutic effect (Rosenthal et al. 1984). Two possible mechanisms have been proposed for the therapeutic effect of bright light. Firstly, bright light could reset the phase of abnormal circadian rhythms seen in depressed patients (Lewy et al. 1984). Secondly, although evening bright light exposure produces a momentary suppression of melatonin, it actually causes a rebound increase in melatonin secretion late in the night (Beck-Friis et al. 1985). The fact that bright light exposure ultimately facilitates melatonin secretion rather than suppressing it is said to be responsible for the therapeutic efficacy of bright light in affective disorders. Hence in the case of PD, bright light may improve the symptoms of PD, not by antagonizing melatonin secretion but by increasing it through a rebound effect.

Indeed, the bright light effect may be indicative of circadian changes in PD. This is supported by the reduced Bmal1 mRNA expression in leukocytes (Cai et al. 2010), although effects in peripheral oscillators do not necessarily allow conclusions on changes in the hypothalamic master clock. The finding that the mouse striatal DA receptors D1R and D2R are under circadian control (Cai et al. 2010), can be seen as an interesting facet in this context, although circadian variations in receptor expression are by no means exceptional features.
9.7 Conclusions

As melatonin exhibits both hypnotic and chronobiotic properties, it has been therapeutically used for treatment of age-related insomnia as well as of other primary and secondary insomnia (Leger et al. 2004; Zhdanova et al. 2001). A recent consensus of the British Association for Psychopharmacology on evidence-based treatment of insomnia, parasomnia, and circadian rhythm sleep disorders concluded that melatonin is the first-choice treatment when a hypnotic is indicated in patients over 55 years (Wilson et al. 2010).

As shown by the binding affinities, half-life, and relative potencies of the different melatonin agonists in the market, it is clear that studies using 2–5 mg melatonin/day are unsuitable to give appropriate comparison with the effect of the abovementioned compounds, which, in addition to being generally more potent than the native molecule, are employed in considerably higher amounts (Cardinali et al. 2011b). Melatonin has a high safety profile and it is usually remarkably well tolerated. In some studies melatonin has been administered to patients at large doses (Weishaupt et al. 2006; Chahbouni et al. 2010; Waldhauser et al. 1984; Voordouw et al. 1992). Therefore, further studies employing melatonin doses in the 100 mg/day are needed to clarify its potential therapeutical implications in humans. From animal studies it is clear that a number of preventive effects of melatonin, like those in neurodegenerative disorders, need high doses of melatonin to become apparent (Cardinali et al. 2010; Srinivasan et al. 2011a, b). If one expects melatonin to be an effective neuroprotector, especially in aged people, it is likely that the low doses of melatonin employed so far are not very beneficial.

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Conflict of Interest None is declared.

References

Acuña-Castroviejo D, Coto-Montes A, Gaia MM, Ortiz GG, Reiter RJ (1997) Melatonin is protective against MPTP-induced striatal and hippocampal lesions. Life Sci 60: L23–L29
Acuña-Castroviejo D, Lopez LC, Escames G, Lopez A, Garcia JA, Reiter RJ (2011) Melatonin-mitochondria interplay in health and disease. Curr Top Med Chem 11:221–240
Adi N, Mash DC, Ali Y, Singer C, Shehadeh L, Papapetropoulos S (2010) Melatonin MT1 and MT2 receptor expression in Parkinson’s disease. Med Sci Monit 16:BR61–BR67
Agrawal R, Tyagi E, Shukla R, Nath C (2009) A study of brain insulin receptors, AChE activity and oxidative stress in rat model of ICV STZ induced dementia. Neuropharmacology 56:779–787
Alam ZI, Jenner A, Daniel SE, Lees AJ, Cairns N, Marsden CD et al (1997) Oxidative DNA damage in the parkinsonian brain: an apparent selective increase in 8-hydroxyguanine levels in substantia nigra. J Neurochem 69:1196–1203
Andersen KN, Shneerson JM (2009) Drug treatment of REM sleep behavior disorder: the use of drug therapies other than clonazepam. J Clin Sleep Med 5:235–239
Andersen KN, Jameison S, Graham AJ, Shneerson JM (2008) REM sleep behaviour disorder treated with melatonin in a patient with Alzheimer’s disease. Clin Neurol Neurosurg 110:492–495
Andrabi SA, Sayeed I, Siemen D, Wolf G, Horn TF (2004) Direct inhibition of the mitochondrial permeability transition pore: a possible mechanism responsible for anti-apoptotic effects of melatonin. FASEB J 18:869–871
Antolin I, Rodriguez C, Sainz RM, Mayo JC, Uria H, Kotler ML et al (1996) Neurohormone melatonin prevents cell damage: effect on gene expression for antioxidant enzymes. FASEB J 10:882–890
Antolin I, Mayo JC, Sainz RM, del Brio ML, Herrera F, Martin V et al (2002) Protective effect of melatonin in a chronic experimental model of Parkinson’s disease. Brain Res 943:163–173
Arends YM, Duyckaerts C, Rozemuller JM, Eikelenboom P, Hauw JJ (2000) Microglia, amyloid and dementia in alzheimer disease. A correlative study. Neurobiol Aging 21:39–47
Asayama K, Yamadera H, Ito T, Suzuki H, Kudo Y, Endo S (2003) Double blind study of melatonin effects on the sleep-wake rhythm, cognitive and non-cognitive functions in Alzheimer type dementia. J Nippon Med Sch 70:334–341
Aurora RN, Zak RS, Maganti RK, Auerbach SH, Casey KR, Chowdhuri S et al (2010) Best practice guide for the treatment of REM sleep behavior disorder (RBD). J Clin Sleep Med 6:85–95
Bach TG, Adler CH, Sue L, Sue LI, Bachalakuri J, Henry-Watson J et al (2009) Unified staging system for Lewy body disorders: correlation with nigrostratal degeneration, cognitive impairment and motor dysfunction. Acta Neuropathol 117:613–634
Beaulieu-Bonneau S, Hudon C (2009) Sleep disturbances in older adults with mild cognitive impairment. Int Psychogeriatr 21:654–666
Beck-Friis J, Kjellman BF, Aperia B, Unden F, von Rosen D, Ljunggren JG et al (1985) Serum melatonin in relation to clinical variables in patients with major depressive disorder and a hypothesis of a low melatonin syndrome. Acta Psychiatr Scand 71:319–330
Beni SM, Kohen R, Reiter RJ, Tan DX, Shohami E (2004) Melatonin-induced neuroprotection after closed head injury is associated with increased brain antioxidants and attenuated late-phase activation of NF-kappa B and AP-1. FASEB J 18:149–151
Benitez-King G, Rios A, Martinez A, Anton-Tay F (1996) In vitro inhibition of Ca2+/calmodulin-dependent kinase II activity by melatonin. Biochim Biophys Acta 1290:191–196
Benitez-King G, Tunez I, Bellon A, Ortiz GG, Anton-Tay F (2003) Melatonin prevents cytoskeletal alterations and oxidative stress induced by okadaic acid in N1E-115 cells. Exp Neurol 182:151–159
Benitez-King G, Ramirez-Rodriguez G, Ortiz L, Meza I (2004) The neuronal cytoskeleton as a potential therapeutical target in neurodegenerative diseases and schizophrenia. Curr Drug Targets CNS Neurol Disord 3:515–533
Billingsley ML, Kincaid RL (1997) Regulated phosphorylation and dephosphorylation of tau protein: effects on microtubule interaction, intracellular trafficking and neurodegeneration. Biochem J 323(Pt 3):577–591
Bovee BF, Silber MH, Ferman TJ (2003) Melatonin for treatment of REM sleep behavior disorder in neurologic disorders: results in 14 patients. Sleep Med 4:281–284
Borah A, Mohanakumar KP (2009) Melatonin inhibits 6-hydroxydopamine production in the brain to protect against experimental parkinsonism in rodents. J Pineal Res 47:293–300
Bordet R, Devos D, Brique S, Toutou Y, Guieu JD, Libersa C et al (2003) Study of circadian melatonin secretion pattern at different stages of Parkinson’s disease. Clin Neuropharmacol 26:65–72
Braak H, Braak E (1995) Staging of Alzheimer’s disease-related neurofibrillary changes. Neurobiol Aging 16:271–278
Braak H, Braak E (1998) Evolution of neuronal changes in the course of Alzheimer’s disease. J Neural Transm Suppl 53:127–140
Braak H, Del Tredici K, Rub U, de Vos RA, Jansen Steur EN, Braak E (2003) Staging of brain pathology related to sporadic Parkinson’s disease. Neurobiol Aging 24:197–211
Brion JP, Anderton BH, Authelet M, Dayanandan R, Leroy K, Lovestone S et al (2001) Neurofibrillary tangles and tau phosphorylation. Biochem Soc Symp 67:81–88
Brito-Armas JM, Baekelandt V, Castro-Hernandez JR, Gonzalez-Hernandez T, Rodriguez M, Castro R (2013) Melatonin prevents dopaminergic cell loss induced by lentiviral vectors expressing A30P mutant alpha-synuclein. Histol Histopathol 28:999–1006
Brusco LI, Marquez M, Cardinali DP (1998a) Melatonin treatment stabilizes chronobiologic and cognitive symptoms in Alzheimer’s disease. Neuroendocrinology 19:111–115
Brusco LI, Marquez M, Cardinali DP (1998b) Monozygotic twins with Alzheimer’s disease treated with melatonin: case report. J Pineal Res 25:260–263
Brzezinski A, Vangel MG, Wurtman RJ, Norrie G, Zhadanova I, Ben-Shushan A et al (2005) Effects of exogenous melatonin on sleep: a meta-analysis. Sleep Med Rev 9:41–50
Bubenik GA, Konturek SJ (2011) Melatonin and aging: prospects for human treatment. J Physiol Pharmacol 62:13–19
Buscemi N, Vandermeer B, Hooton N, Pandya R, Tjosvold L, Hartling L et al (2006) Efficacy and safety of exogenous melatonin for secondary sleep disorders and sleep disorders accompanying sleep restriction: meta-analysis. BMJ 332:385–393
Cai Y, Liu S, Sothern RB, Xu S, Chan P (2010) Expression of clock genes Per1 and Bmal1 in total leukocytes in health and Parkinson’s disease. Eur J Neurol 17:550–554
Cardinali DP, Lynch HJ, Wurtman RJ (1972) Binding of melatonin to human and rat plasma proteins. Endocrinology 91:1213–1218
Cardinali DP, Ritta MN, Fuentes AM, Gimeno MF, Gimeno AL (1980) Prostaglandin E release by rat medial basal hypothalamus in vitro. Inhibition by melatonin at submicromolar concentrations. Eur J Pharmacol 67:151–153
Cardinali DP, Brusco LI, Liberczuk C, Furio AM (2002) The use of melatonin in Alzheimer’s disease. Neuroendocrinol Lett 23(Suppl 1):20–23
Cardinali DP, Pandi-Perumal SR, Niles LP (2008) Melatonin and its receptors: biological function in circadian sleep-wake regulation. In: Monti JM, Pandi-Perumal SR, Sinton CM (eds) Neurochemistry of sleep and wakefulness. Cambridge University Press, Cambridge, pp 283–314
Cardinali DP, Furio AM, Brusco LI (2010) Clinical aspects of melatonin intervention in Alzheimer’s disease progression. Curr Neuropharmacol 8:218–227
Cardinali DP, Cano P, Jimenez-Ortega V, Esquifino AI (2011a) Melatonin and the metabolic syndrome. Physiopathologic and therapeutical implications. Neuroendocrinology 93:133–142
Cardinali DP, Furio AM, Brusco LI (2011b) The use of chronobiotics in the resynchronization of the sleep/wake cycle. Therapeutical application in the early phases of Alzheimer’s disease. Recent Patents Endocr Metab Immune Drug Discov 5:80–90
Cardinali DP, Vigo DE, Olivar N, Vidal MF, Furio AM, Brusco LI (2012a) Therapeutic application of melatonin in mild cognitive impairment. Am J Neurodegener Dis 1:280–291
Cardinali DP, Srinivasan V, Brzezinski A, Brown GM (2012b) Melatonin and its analogs in insomnia and depression. J Pineal Res 52:365–375
Carneiro RC, Reiter RJ (1998) Delta-aminolevulinic acid-induced lipid peroxidation in rat kidney and liver is attenuated by melatonin: in vitro and in vivo study. J Pineal Res 24:131–136
Carta MG, Hardoy MC, Dell’Osso L, Carpiniello B (2004) Tardive dyskinesia: review of the literature. Clin Ter 155:127–133
Catala MD, Canete-Nicolás C, Iraidi A, Tarazona PJ, Tormos JM, Pascual-Leone A (1997) Melatonin levels in Parkinson’s disease: drug therapy versus electrical stimulation of the internal globus pallidus. Exp Gerontol 32:553–558
Caumo W, Levandovski R, Hidalgo MP (2009) Preoperative anxiolytic effect of melatonin and clonidine on postoperative pain and morphine consumption in patients undergoing abdominal hysterectomy: a double-blind, randomized, placebo-controlled study. J Pain 10:100–108
Cazzola R, Rondanelli M, Faliva M, Cestaro B (2012) Effects of DHA-phospholipids, melatonin and tryptophan supplementation on erythrocyte membrane physico-chemical properties in elderly patients suffering from mild cognitive impairment. Exp Gerontol 47:974–978
Chahbouni M, Escames G, Venegas C, Sevilla B, Garcia JA, Lopez LC et al (2010) Melatonin treatment normalizes plasma pro-inflammatory cytokines and nitrosative/oxidative stress in patients suffering from Duchenne muscular dystrophy. J Pineal Res 48:282–289
Chan AS, Lai FP, Lo RK, Voyno-Yasenetskaya TA, Stanbridge EJ, Wong YH (2002) Melatonin mt1 and MT2 receptors stimulate c-Jun N-terminal kinase via pertussis toxin-sensitive and -insensitive G proteins. Cell Signal 14:249–257
Chang CF, Huang HJ, Lee HC, Hung KC, Wu RT, Lin AM (2012) Melatonin attenuates kainic acid-induced neurotoxicity in mouse hippocampus via inhibition of autophagy and alpha-synuclein aggregation. J Pineal Res 52:312–321
Cho S, Joh TH, Baik HH, Dibinis C, Volpe BT (1997) Melatonin administration protects CA1 hippocampal neurons after transient forebrain ischemia in rats. Brain Res 755:335–338
Chuang JI, Mohan N, Meltz ML, Reiter RJ (1996) Effect of melatonin on NF-kappa-B DNA-binding activity in the rat spleen. Cell Biol Int 20:687–692
Claustrat B, Brun J, Chazot G (2005) The basic physiology and pathophysiology of melatonin. Sleep Med Rev 9:11–24
Clay E, Falissard B, Moore N, Toumi M (2013) Contribution of prolonged-release melatonin and anti-benzodiazepine campaigns to the reduction of benzodiazepine and Z-drugs consumption in nine European countries. Eur J Clin Pharmacol 69:1–10
Cochen V, Arbus C, Soto ME, Villars H, Tiberge M, Montemayor T et al (2009) Sleep disorders and their impacts on healthy, dependent, and frail older adults. J Nutr Health Aging 13:322–329
Cohen-Mansfield J, Garfinkel D, Lipson S (2000) Melatonin for treatment of sundowning in elderly persons with dementia – a preliminary study. Arch Gerontol Geriatr 31:65–76
Combadiere C, Feumi C, Raoul W, Keller N, Rodero M, Pezard A et al (2007) CX3CR1-dependent subretinal microglia cell accumulation is associated with cardinal features of age-related macular degeneration. J Clin Invest 117:2920–2928
Costantino G, Cuzzocrea S, Mazzon E, Caputi AP (1998) Protective effects of melatonin in zymosan-activated plasma-induced paw inflammation. Eur J Pharmacol 363:57–63
Cuzzocrea S, Zingarelli B, Gilad E, Hake P, Salzman AL, Szabo C (1997) Protective effect of melatonin in carrageenan-induced models of local inflammation: relationship to its inhibitory effect on nitric oxide production and its peroxynitrite scavenging activity. J Pineal Res 23:106–116
Dagan Y, Zisapel N, Nof D, Laudon M, Atsmon J (1997) Rapid reversal of tolerance to benzodiazepine hypnotics by treatment with oral melatonin: a case report. Eur Neuropsychopharmacol 7:157–160
Davies L, Wolska B, Hilbich C, Multhaup G, Martins R, Simms G et al (1988) A4 amyloid protein deposition and the diagnosis of Alzheimer’s disease: prevalence in aged brains determined by immunocytochemistry compared with conventional neuropathologic techniques. Neurology 38:1688–1693
de Jonghe A, Korevaar JC, van Munster BC, de Rooij SE (2010) Effectiveness of melatonin treatment on circadian rhythm disturbances in dementia. Are there implications for delirium? A systematic review. Int J Geriatr Psychiatry 25:1201–1208
Deng YQ, Xu GG, Duan P, Zhang Q, Wang JZ (2005) Effects of melatonin on wortmannin-induced tau hyperphosphorylation. Acta Pharmacol Sin 26:519–526
Deng WG, Tang ST, Tseng HP, Wu KK (2006) Melatonin suppresses macrophage cyclooxygenase-2 and inducible nitric oxide synthase expression by inhibiting p52 acetylation and binding. Blood 108:518–524
Dexter DT, Carter CJ, Wells FR, Javoy-Agid F, Agid Y, Lees A et al (1989) Basal lipid peroxidation in substantia nigra is increased in Parkinson’s disease. J Neurochem 52:381–389
Dodd S, Maes M, Anderson G, Dean OM, Moylan S, Berk M (2013) Putative neuroprotective agents in neuropsychiatric disorders. Prog Neuropsychopharmacol Biol Psychiatry 42:135–145
Donnelly PS, Caragounis A, Du T, Laughton KM, Volitakis I, Cherny RA et al (2008) Selective intracellular release of copper and zinc ions from bis(thiosemicarbazono) complexes reduces levels of Alzheimer disease amyloid-beta peptide. J Biol Chem 283:4568–4577
Dowling GA, Mastick J, Colling E, Carter JH, Singer CM, Aminoff MJ (2005) Melatonin for sleep disturbances in Parkinson’s disease. Sleep Med 6:459–466
Dowling GA, Burr RL, Van Someren EJ, Hubbard EM, Luxenberg JS, Mastick J et al (2008) Melatonin and bright-light treatment for rest-activity disruption in institutionalized patients with Alzheimer’s disease. J Am Geriatr Soc 56:239–246
Dragicevic N, Copes N, O’Neal-Moffitt G, Jin J, Buzzo R, Manczar M et al (2011) Melatonin treatment restores mitochondrial function in Alzheimer’s mice: a mitochondrial protective role of melatonin membrane receptor signaling. J Pineal Res 51:75–86
Dubocovich ML, Delargrange P, Krause DN, Sugden D, Cardinali DP; Olcese J (2010) International Union of Basic and Clinical Pharmacology. LXXV. Nomenclature, classification, and pharmacology of G protein-coupled melatonin receptors. Pharmacol Rev 62:343–380
Erol FS, Topsakal C, Ozveren MF, Kaplan M, Ilhan N, Ozercan IH et al (2004) Protective effects of melatonin and vitamin E in brain damage due to gamma radiation: an experimental study. Neurosurg Rev 27:65–69
Escames G, Acuña-Castroviejo D, Vives F (1996) Melatonin-dopamine interaction in the striatal projection area of sensorimotor cortex in the rat. Neuroreport 7:597–600
Escames G, Leon J, Lopez LC, Acuña-Castroviejo D (2004) Mechanisms of N-methyl-D-aspartate receptor inhibition by melatonin in the rat striatum. J Neuroendocrinol 16:929–935
Facchini G, Hidestrand M, von Bahr C, Tybring G (2001) Cytochrome P450 isoforms involved in melatonin metabolism in human liver microsomes. Eur J Clin Pharmacol 56:881–888
Fahn S, Cohen G (1992) The oxidant stress hypothesis in Parkinson’s disease: evidence supporting it. Ann Neurol 32:804–812
Fainstein I, Bonetto A, Brusco LI, Cardinali DP (1997) Effects of melatonin in elderly patients with sleep disturbance. A pilot study. Curr Ther Res 58:990–1000
Farias ST, Mungas D, Reed BR, Harvey D, DeCarli C (2009) Progression of mild cognitive impairment to dementia in clinic- vs community-based cohorts. Arch Neurol 66:1151–1157
Feng Z, Chang Y, Cheng Y, Zhang BL, Qu ZW, Qin C et al (2004a) Melatonin alleviates behavioral deficits associated with apoptosis and cholinergic system dysfunction in the APP 695 transgenic mouse model of Alzheimer’s disease. J Pineal Res 37:129–136
Feng Z, Cheng Y, Zhang JT (2004b) Long-term effects of melatonin or 17 beta-estradiol on improving spatial memory performance in cognitively impaired, ovariectomized adult rats. J Pineal Res 37:198–206
Fernandez-Bachiller MI, Perez C, Campillo NE, Paez JA, Gonzalez-Munoz GC, Usan P et al (2009) Tacrine-melatonin hybrids as multifunctional agents for Alzheimer’s disease, with cholinergic, antioxidant, and neuroprotective properties. ChemMedChem 4:828–841
Fertl E, Auff E, Doppelbauer A, Waldhauser F (1993) Circadian secretion pattern of melatonin in de novo parkinsonian patients: evidence for phase-shifting properties of l-dopa. J Neural Transm Park Dis Dement Sect 5:227–234
Fornai F, Soldani P, Lazzeri G, di Poggio AB, Biagioni F, Fulseri F et al (2005) Neuronal inclusions in degenerative disorders: do they represent static features or a key to understand the dynamics of the disease? Brain Res Bull 65:275–290
Fotuhi M, Hachinski V, Whitehouse PJ (2009) Changing perspectives regarding late-life dementia. Nat Rev Neurol 5:649–658
Furio AM, Cutrera RA, Castillo TV, Perez LS, Riccio P, Caccuri RL et al (2002) Effect of melatonin on changes in locomotor activity rhythm of Syrian hamsters injected with beta amyloid peptide 25–35 in the suprachiasmatic nuclei. Cell Mol Neurobiol 22:699–709
Furio AM, Brusco LI, Cardinali DP (2007) Possible therapeutic value of melatonin in mild cognitive impairment. A retrospective study. J Pineal Res 43:404–409
Furio AM, Fontao R, Falco N, Ruiz JL, Caccuri RL, Cardinali DP (2008) Neuroprotective effect of melatonin on glucocorticoid toxicity in the rat hippocampus. Open Physiol J 1:23–27
Galano A, Tan DX, Reiter RJ (2011) Melatonin as a natural ally against oxidative stress: a physicochemical examination. J Pineal Res 51:1–16
Garfinkel D, Zisapel N, Wainstein J, Laudon M (1999) Facilitation of benzodiazepine discontinuation by melatonin: a new clinical approach. Arch Intern Med 159:2456–2460
Garzon C, Guerrero JM, Aramburu O, Guzman T (2009) Effect of melatonin administration on sleep, behavioral disorders and hypnotic drug discontinuation in the elderly: a randomized, double-blind, placebo-controlled study. Aging Clin Exp Res 21:38–42

Gehrman PR, Connor DJ, Martin JL, Shochat T, Corey-Bloom J, Ancoli-Israel S (2009) Melatonin fails to improve sleep or agitation in double-blind randomized placebo-controlled trial of institutionalized patients with Alzheimer disease. Am J Geriatr Psychiatry 17:166–169

Gibson GE, Starkov A, Blass JP, Ratan RR, Bea MF (2010) Cause and consequence: mitochondrial dysfunction initiates and propagates neuronal dysfunction, neuronal death and behavioral abnormalities in age-associated neurodegenerative diseases. Biochim Biophys Acta 1802:122–134

Giusti P, Lipartiti M, Franceschini D, Schiavo N, Floreani M, Manev H (1996) Neuroprotection by melatonin from kainate-induced excitotoxicity in rats. FASEB J 10:891–896

Golombek DA, Pevet P, Cardinali DP (1996) Melatonin effects on behavior: possible mediation by the central GABAergic system. Neurosci Biobehav Rev 20:403–412

Gomez-Ramos A, Diaz-Nido J, Smith MA, Perry G, Avila J (2003) Effect of the lipid peroxidation product acrolein on tau phosphorylation in neural cells. J Neurosci Res 71:863–870

Grundman M, Petersen RC, Ferris SH, Thomas RG, Aisen PS, Bennett DA et al (2004) Mild cognitive impairment can be distinguished from Alzheimer disease and normal aging for clinical trials. Arch Neurol 61:59–66

Guernonprez L, Ducrocq C, Gaudry-Talarmain YM (2001) Inhibition of acetylcholine synthesis and tyrosine nitration induced by peroxynitrite are differentially prevented by antioxidants. Mol Pharmacol 60:838–846

Harada S, Fujii C, Hayashi A, Ohkoshi N (2001) An association between idiopathic Parkinson’s disease and polymorphisms of phase II detoxification enzymes: glutathione S-transferase M1 and quinone oxidoreductase 1 and 2. Biochem Biophys Res Commun 288:887–892

Hardeland R, Tan DX, Reiter RJ (2009) Kyuramines, metabolites of melatonin and other indoles: the resurrection of an almost forgotten class of biogenic amines. J Pineal Res 47:109–126

Hardeland R, Cardinali DP, Srinivasan V, Spence DW, Brown GM, Pandi-Perumal SR (2011) Melatonin – a pleiotropic, orchestrating regulator molecule. Prog Neurobiol 93:350–384

Harper DG, Stopa EG, McKee AC, Satlin A, Harlan PC, Goldstein R et al (2001) Differential circadian rhythm disturbances in men with Alzheimer disease and frontotemporal degeneration. Arch Gen Psychiatry 58:353–360

Hartter S, Ursing C, Morita S, Tybring G, von Bahr C, Christensen M et al (2001) Orally given melatonin may serve as a probe drug for cytochrome P<sub>450</sub>1A2 activity in vivo: a pilot study. Clin Pharmacol Ther 70:10–16

Herraiz T, Guilien H (2011) Inhibition of the bioactivation of the neurotoxin MPTP by antioxidants, redox agents and monoamine oxidase inhibitors. Food Chem Toxicol 49:1773–1781

Hsiao K, Chapman P, Nilsen S, Eckman C, Harigaya Y, Younkin S et al (1996) Correlative memory deficits, Aβ elevation, and amyloid plaques in transgenic mice. Science 274:99–102

Iqbal K, Alonso AC, Chen S, Chohan MO, El-Akkad E, Gong CX et al (2005) Tau pathology in Alzheimer disease and other tauopathies. Biochim Biophys Acta 1739:198–210

Jean-Louis G, Zizi F, von Gizycki H, Taub H (1998a) Effects of melatonin in two individuals with Alzheimer’s disease. Percept Mot Skills 87:331–339

Jean-Louis G, von Gizycki H, Zizi F (1998b) Melatonin effects on sleep, mood, and cognition in elderly with mild cognitive impairment. J Pineal Res 25:177–183

Jiao S, Wu MM, Hu CL, Zhang ZH, Mei YA (2004) Melatonin receptor agonist 2-iodomelatonin prevents apoptosis of cerebellar granule neurons via K<sup>+</sup> current inhibition. J Pineal Res 36:109–116

Jimenez-Ortega V, Cano P, Cardinali DP, Esquifino AI (2009) 24-Hour variation in gene expression of redox pathway enzymes in rat hypothalamus: effect of melatonin treatment. Redox Rep 14:132–138

Jimenez-Ortega V, Cano P, Scacchi PA, Cardinali DP, Esquifino AI (2011) Cadmium-induced disruption in 24-h expression of clock and redox enzyme genes in rat medial basal hypothalamus. Prevention by melatonin. Front Neurol (Sleep Chronobiol) 2:art13-1-19
Johnson EJ, Vishwanathan R, Johnson MA, Hausman DB, Davey A, Scott TM et al (2013) Relationship between serum and brain carotenoids, alpha-tocopherol, and retinol concentrations and cognitive performance in the oldest old from the Georgia Centenarian Study. J Aging Res 2013:951786
Jou MJ (2011) Melatonin preserves the transient mitochondrial permeability transition for protection during mitochondrial Ca$^{2+}$ stress in astrocyte. J Pineal Res 50:427–435
Kabadi SV, Maher TJ (2010) Posttreatment with uridine and melatonin following traumatic brain injury reduces edema in various brain regions in rats. Ann NY Acad Sci 1199:105–113
Kenyon CJ (2010) The genetics of ageing. Nature 464:504–512
Khandelwal N, Simpson J, Taylor G, Rafrique S, Whitehouse A, Hiscox J et al (2011) Nucleolar NF-kappaB/RelA mediates apoptosis by causing cytoplasmic relocalization of nucleophosmin. Cell Death Differ 18:1889–1903
Khatoon S, Grundke-Iqbal I, Iqbal K (1992) Brain levels of microtubule-associated protein tau are elevated in Alzheimer’s disease: a radioimmuno-slot-blot assay for nanograms of the protein. J Neurochem 59:750–753
Kilanczyk E, Bryszewska M (2003) The effect of melatonin on antioxidant enzymes in human diabetic skin fibroblasts. Cell Mol Biol Lett 8:333–336
Kilic E, Ozdemir YG, Bolay H, Kelestimur H, Dalkara T (1999) Pinealectomy aggravates and melatonin administration attenuates brain damage in focal ischemia. J Cereb Blood Flow Metab 19:511–516
Klaffke S, Staedt J (2006) Sundowning and circadian rhythm disorders in dementia. Acta Neurol Belg 106:168–175
Klongpanichapak S, Phansuwan-Pujito P, Ebadi M, Govitrapong P (2008) Melatonin inhibits amphetamine-induced increase in alpha-synuclein and decrease in phosphorylated tyrosine hydroxylase in SK-N-SH cells. Neurosci Lett 436:309–313
Koh PO (2011) Melatonin prevents down-regulation of astrocytic phosphoprotein PEA-15 in ischemic brain injury. J Pineal Res 51:381–386
Koller WC (1996) Management of motor fluctuations in Parkinson’s disease. Eur Neurol 36(Suppl 1):43–48
Kunz D, Bes F (1997) Melatonin effects in a patient with severe REM sleep behavior disorder: case report and theoretical considerations. Neuropsychobiology 36:211–214
Kunz D, Bes F (1999) Melatonin as a therapy in REM sleep behavior disorder patients: an open-labeled pilot study on the possible influence of melatonin on REM-sleep regulation. Mov Disord 14:507–511
Kunz D, Bineau S, Maman K, Milea D, Toumi M (2012) Benzodiazepine discontinuation with prolonged-release melatonin: hints from a German longitudinal prescription database. Expert Opin Pharmacother 13:9–16
Lahiri DK, Ghosh C (1999) Interactions between melatonin, reactive oxygen species, and nitric oxide. Ann NY Acad Sci 893:325–330
Lahiri DK, Chen D, Ge YW, Bondy SC, Sharman EH (2004) Dietary supplementation with melatonin reduces levels of amyloid beta-peptides in the murine cerebral cortex. J Pineal Res 36:224–231
Lardone PJ, Guerrero JM, Fernandez-Santos JM, Rubio A, Martin-Lacave I, Carrillo-Vico A (2011) Melatonin synthesized by T lymphocytes as a ligand of the retinoic acid-related orphan receptor. J Pineal Res 51:454–462
Lau WW, Ng JK, Lee MM, Chan AS, Wong YH (2012) Interleukin-6 autocrine signaling mediates melatonin MT$_1$/MT$_2$ receptor-induced STAT3 Tyr$	ext{705}$ phosphorylation. J Pineal Res 52:477–489
Lee EJ, Wu TS, Lee MY, Chen TY, Tsai YY, Chuang JJ et al (2004) Delayed treatment with melatonin enhances electrophysiological recovery following transient focal cerebral ischemia in rats. J Pineal Res 36:33–42
Leger D, Laudon M, Zisapel N (2004) Nocturnal 6-sulfatoxymelatonin excretion in insomnia and its relation to the response to melatonin replacement therapy. Am J Med 116:91–95
Leon-Blanco MM, Guerrero JM, Reiter RJ, Pozo D (2004) RNA expression of human telomerase subunits TR and TERT is differentially affected by melatonin receptor agonists in the MCF-7 tumor cell line. Cancer Lett 216:73–80
Levoye A, Dam J, Ayoub MA, Guillaume JL, Couturier C, Delargrange P et al (2006) The orphan GPR50 receptor specifically inhibits MT1 melatonin receptor function through heterodimerization. EMBO J 25:3012–3023
Lewy AJ, Sack RA, Singer CL (1984) Assessment and treatment of chronobiologic disorders using plasma melatonin levels and bright light exposure: the clock-gate model and the phase response curve. Psychopharmacol Bull 20:561–565
Li SP, Deng YQ, Wang XC, Wang YP, Wang JZ (2004) Melatonin protects SH-SY5Y neuroblastoma cells from calyculin A-induced neurofilament impairment and neurotoxicity. J Pineal Res 36:186–191
Li XC, Wang ZF, Zhang JX, Wang Q, Wang JZ (2005) Effect of melatonin on calyculin A-induced tau hyperphosphorylation. Eur J Pharmacol 510:25–30
Lin AM, Fang SF, Chao PL, Yang CH (2007) Melatonin attenuates arsenite-induced apoptosis in rat brain: involvement of mitochondrial and endoplasmic reticulum pathways and aggregation of alpha-synuclein. J Pineal Res 43:163–171
Litvinenko IV, Kraskov IV, Tikhomirova OV (2012) Sleep disorders in Parkinson’s disease without dementia: a randomized controlled study of melatonin and clonazepam. Zh Nevrol Psikhiatr Im S S Korsakova 112:26–30
Liu SJ, Wang JZ (2002) Alzheimer-like tau phosphorylation induced by wortmannin in vivo and its attenuation by melatonin. Acta Pharmacol Sin 23:183–187
Liu RY, Zhou JN, van Heerikhuize J, Hofman MA, Swaab DF (1999) Decreased melatonin levels in postmortem cerebrospinal fluid in relation to aging, Alzheimer’s disease, and apolipoprotein E-epsilon4 genotype. J Clin Endocrinol Metab 84:323–327
Louzada PR, Paula Lima AC, Mendonca-Silva DL, Noel F, De Mello FG, Ferreira ST (2004) Taurine attenuates the neurotoxicity of beta-amyloid and glutamate receptor agonists: activation of GABA receptors and possible implications for Alzheimer’s disease and other neurological disorders. FASEB J 18:511–518
Lovell MA, Xiong S, Xie C, Davies P, Markesbery WR (2004) Induction of hyperphosphorylated tau in primary rat cortical neuron cultures mediated by oxidative stress and glycogen synthase kinase-3. J Alzheimers Dis 6:659–671
Magri F, Locatelli M, Balza G, Molla G, Cuzzoni G, Fioravanti M et al (1997) Changes in endocrine circadian rhythms as markers of physiological and pathological brain aging. Chronobiol Int 14:385–396
Maguire-Zeiss KA, Federoff HJ (2010) Future directions for immune modulation in neurodegenerative disorders: focus on Parkinson’s disease. J Neural Transm 117:1019–1025
Mahlberg R, Walthier S (2007) Actigraphy in agitated patients with dementia. Monitoring treatment outcomes. Z Gerontol Geriatr 40:178–184
Mahlberg R, Kunz D, Sutej I, Kuhl KP, Hellweg R (2004) Melatonin treatment of day-night rhythm disturbances and sundowning in Alzheimer disease: an open-label pilot study using actigraphy. J Clin Psychopharmacol 24:456–459
Manev H, Uz T, Kharlamov A, Joo JY (1996) Increased brain damage after stroke or excitotoxic seizures in melatonin-deficient rats. FASEB J 10:1546–1551
Matsumbara E, Bryant-Thomas T, Pacheco QI, Henry TL, Poeggeler B, Herbert D et al (2003) Melatonin increases survival and inhibits oxidative and amyloid pathology in a transgenic model of Alzheimer’s disease. J Neurochem 85:1101–1108
Mayo JC, Sainz RM, Uria H, Antolin I, Esteban MM, Rodriguez C (1998) Melatonin prevents apoptosis induced by 6-hydroxydopamine in neuronal cells: implications for Parkinson’s disease. J Pineal Res 24:179–192
McCarter SJ, Boswell CL, St Louis EK, Dueffert LG, Slocumb N, Boeve BF et al (2013) Treatment outcomes in REM sleep behavior disorder. Sleep Med 14:237–242
Medeiros CA, de Bruin CPF, Lopes LA, Magalhaes MC, de Lourdes SM, de Bruin VM (2007) Effect of exogenous melatonin on sleep and motor dysfunction in Parkinson’s disease. A randomized, double blind, placebo-controlled study. J Neurol 254:459–464
Mishima K, Tozawa T, Satoh K, Matsumoto Y, Hishikawa Y, Okawa M (1999) Melatonin secretion rhythm disorders in patients with senile dementia of Alzheimer’s type with disturbed sleep-waking. Biol Psychiatry 45:417–421
Mishima K, Okawa M, Hozumi S, Hishikawa Y (2000) Supplementary administration of artificial bright light and melatonin as potent treatment for disorganized circadian rest-activity and dys-functional autonomic and neuroendocrine systems in institutionalized demented elderly persons. Chronobiol Int 17:419–432
Mohan N, Sadeghi K, Reiter RJ, Meltz ML (1995) The neurohormone melatonin inhibits cytokine, mitogen and ionizing radiation induced NF-kappa B. Biochem Mol Biol Int 37:1063–1070
Monti JM, Alvarino F, Cardinali DP, Savio I, Pintos A (1999) Polysomnographic study of the effect of melatonin on sleep in elderly patients with chronic primary insomnia. Arch Gerontol Geriatr 28:85–98
Montilla P, Feijoo M, Munoz MC, Munoz-Castaneda JR, Bujalance I, Tunez I (2003) Effect of melatonin on the oxidative stress in N1E-115 cells is not mediated by mt1 receptors. J Physiol Biochem 59:263–268
Montilla-Lopez P, Munoz-Agueda MC, Feijoo LM, Munoz-Castaneda JR, Bujalance-Arenas I, Tunez-Finana I (2002) Comparison of melatonin versus vitamin C on oxidative stress and antioxidant enzyme activity in Alzheimer’s disease induced by okadaic acid in neuroblastoma cells. Eur J Pharmacol 451:237–243
Mulchahey JJ, Goldwater DR, Zemlan FP (2004) A single blind, placebo controlled, across groups dose escalation study of the safety, tolerability, pharmacokinetics and pharmacodynamics of the melatonin analog beta-methyl-6-chloromelatonin. Life Sci 75:1843–1856
Naskar A, Manivasagam T, Chakraborty J, Singh R, Thomas B, Dhanasekaran M et al (2013) Melatonin synergizes with low doses of L-DOPA to improve dendritic spine density in the mouse striatum in experimental Parkinsonism. J Pineal Res 55:304–312
Nelson PT, Alafuzoff I, Bigio EH, Bouras C, Braak H, Cairns NJ et al (2012) Correlation of Alzheimer disease neuropathologic changes with cognitive status: a review of the literature. J Neuropathol Exp Neurol 71:362–381
Nickkholgh A, Schneider H, Sobirey M, Venetz WP, Hinz U, le Pelzl H et al (2011) The use of high-dose melatonin in liver resection is safe: first clinical experience. J Pineal Res 50:381–388
Nosjean O, Ferro M, Coge F, Beauverger P, Henlin JM, Lefoulon F et al (2000) Identification of the melatonin-binding site MT1 as the quinone reductase 2. J Biol Chem 275:31311–31317
Ohashi Y, Okamoto N, Uchida K, Iyo M, Mori N, Morita Y (1999) Daily rhythm of serum melatonin levels and effect of light exposure in patients with dementia of the Alzheimer’s type. Biol Psychiatry 45:1646–1652
Olanow CW (1992) An introduction to the free radical hypothesis in Parkinson’s disease. Ann Neurol 32(Suppl):S2–S9
Olanow CW, Brin MF, Obeso JA (2000) The role of deep brain stimulation as a surgical treatment for Parkinson’s disease. Neurology 55:S60–S66
Olcense JM, Cao C, Mori T, Mamcarz MB, Maxwell A, Runfeldt MJ et al (2009) Protection against cognitive deficits and markers of neurodegeneration by long-term oral administration of melatonin in a transgenic model of Alzheimer disease. J Pineal Res 47:82–96
Olivieri G, Hess C, Savaskan E, Ly C, Meier F, Baysang G et al (2001) Melatonin protects SHSY5Y neuroblastoma cells from cobalt-induced oxidative stress, neurotoxicity and increased beta-amyloid secretion. J Pineal Res 31:320–325
Onuki J, Almeida EA, Medeiros MH, Di MP (2005) Inhibition of 5-aminolevulinic acid-induced DNA damage by melatonin, N\(^{\alpha}\)-acetyl-\(N^{\beta}\)-formyl-5-methoxykynuramine, quercetin or resveratrol. J Pineal Res 38:107–115
Pablos MI, Reiter RJ, Chuang JI, Ortiz GG, Guerrero JM, Sewerynek E et al (1997) Acutely administered melatonin reduces oxidative damage in lung and brain induced by hyperbaric oxygen. J Appl Physiol 83:354–358
Pablos MI, Reiter RJ, Ortiz GG, Guerrero JM, Agapito MT, Chuang JI et al (1998) Rhythms of glutathione peroxidase and glutathione reductase in brain of chick and their inhibition by light. Neurochem Int 32:69–75
Pandi-Perumal SR, Seils LK, Kayumov L, Ralph MR, Lowe A, Moller H et al (2002) Senescence, sleep, and circadian rhythms. Ageing Res Rev 1:559–604
Rinne Reiter Reiter Rajaratnam Radogna Qui Princ

Pandig Perumal SR, BaHammam AS, Brown GM, Spence DW, Bharti VK, Kaur C et al (2013)
Melatonin antioxidative defense: therapeutical implications for aging and neurodegenerative processes. Neurotox Res 23(3):267–300

Pappolla M, Bozner P, Soto C, Shao H, Robakis NK, Zagorski M et al (1998) Inhibition of Alzheimer beta-fibrillogenesis by melatonin. J Biol Chem 273:7185–7188

Pappolla MA, Chyan YJ, Poeggeler B, Frangione B, Wilson G, Ghiso J et al (2000) An assessment of the antioxidant and the antiamyloidogenic properties of melatonin: implications for Alzheimer’s disease. J Neural Transm 107:203–231

Park SY, Jin ML, Kim YH, Kim Y, Lee SJ (2012) Anti-inflammatory effects of aromatic-turmerone through blocking of NF-kappaB, JNK, and p38 MAPK signaling pathways in amyloid beta-stimulated microglia. Int Immunopharmacol 14:13–20

Peck JS, LeGoff DB, Ahmed I, Goebert D (2004) Cognitive effects of exogenous melatonin administration in elderly persons: a pilot study. Am J Geriatr Psychiatry 12:432–436

Peng TL, Hsiao CW, Reiter RJ, Tanaka M, Lai YK, Jou MJ (2012) mtDNA T8993G mutation-induced mitochondrial complex V inhibition augments cardiolipin-dependent alterations in mitochondrial dynamics during oxidative, Ca2+, and lipid insults in NARP cybrids: a potential therapeutic target for melatonin. J Pineal Res 52:93–106

Peschke E, Muhlbauer E, Musshoff U, Csernus VJ, Chankiewitz E, Peschke D (2002) Receptor (MT1) mediated influence of melatonin on cAMP concentration and serotonin secretion cells INS-1. J Pineal Res 33:63–71

Poeggeler B, Miravalle L, Zagorski MG, Winsiewski T, Chyan YJ, Zhang Y et al (2001) Melatonin reverses the profibrillogenic activity of apolipoprotein E; on the Alzheimer amyloid Abeta peptide. Biochemistry 40:14995–15001

Poliantri AH, Esquifino AI, Cano P, Jimenez V, Lafuente A, Cardinali DP et al (2006) In vivo protective effect of melatonin on cadmium-induced changes in redox balance and gene expression in rat hypothalamus and anterior pituitary. J Pineal Res 41:238–246

Price JL, Morris JC (1999) Tangles and plaques in nondemented aging and “preclinical” Alzheimer’s disease. Ann Neurol 45:358–368

Princ F, Juknat AA, Maxit AG, Cardalda C, Battle A (1997) Melatonin’s antioxidant protection against delta-aminolevulinic acid-induced oxidative damage in rat cerebellum. J Pineal Res 23:40–46

Quinn J, Kulhanek D, Nowlin J, Jones R, Pratico D, Rokach J et al (2005) Chronic melatonin therapy fails to alter amyloid burden or oxidative damage in old Tg2576 mice: implications for clinical trials. Brain Res 1037:209–213

Radogna F, Diederich M, Gibelli L (2010) Melatonin: a pleiotropic molecule regulating inflammation. Biochem Pharmacol 80:1844–1852

Rajaratnam SM, Polymeropoulos MH, Fisher DM, Roth T, Scott C, Birznieks G et al (2009) Melatonin agonist tasmelteon (VEC-162) for transient insomnia after sleep-time shift: two randomised controlled multicentre trials. Lancet 373:482–491

Reiter RJ, Garcia JJ, Pie J (1998) Oxidative toxicity in models of neurodegeneration: responses to melatonin. Restor Neurol Neurosci 12:135–142

Reiter RJ, Paredes SD, Manchester LC, Tan DX (2009) Reducing oxidative/nitrosative stress: a newly-discovered genre for melatonin. Crit Rev Biochem Mol Biol 44:175–200

Reiter RJ, Manchester LC, Tan DX (2010) Neurotoxins: free radical mechanisms and melatonin protection. Curr Neuropharmacol 8:194–210

Riemersma-van Lek RF, Swaaf DF, Twisk J, Hol EM, Hoogendijk WJ, Van Someren EJ (2008) Effect of bright light and melatonin on cognitive and noncognitive function in elderly residents of group care facilities: a randomized controlled trial. JAMA 299:2642–2655

Rinne JO, Laine M, Hiltunen J, Erkinjuntti T (2003) Semantic decision making in early probable AD: a PET activation study. Brain Res Cogn Brain Res 18:89–96

Rivera-Bermudez MA, Gerdin MJ, Earnest DJ, Dubocovich ML (2003) Regulation of basal rhythmicity in protein kinase C activity by melatonin in immortalized rat suprachiasmatic nucleus cells. Neurosci Lett 346:37–40
Rodriguez C, Mayo JC, Sainz RM, Antolin I, Herrera F, Martin V et al (2004) Regulation of antioxidant enzymes: a significant role for melatonin. J Pineal Res 36:1–9
Rondanelli M, Opizzi A, Faliva M, Mozzoni M, Antoniello N, Cazzola R et al (2012) Effects of a diet integration with an oily emulsion of DHA-phospholipids containing melatonin and tryptophan in elderly patients suffering from mild cognitive impairment. Nutr Neurosci 15:46–54
Rosales-Corral S, Tan DX, Reiter RJ, Valdivia-Velazquez M, Martinez-Barboza G, Acosta-Martinez JP et al (2003) Orally administered melatonin reduces oxidative stress and proinflammatory cytokines induced by amyloid-beta peptide in rat brain: a comparative, in vivo study versus vitamin C and E. J Pineal Res 35:80–84
Rosales-Corral SA, Acuña-Castroviejo D, Coto-Montes A, Boga JA, Manchester LC, Fuentes-Broto L et al (2012) Alzheimer’s disease: pathological mechanisms and the beneficial role of melatonin. J Pineal Res 52:167–202
Rosenthal NE, Sack DA, Gillin JC, Lewy AJ, Goodwin FK, Daventport Y et al (1984) Seasonal affective disorder. A description of the syndrome and preliminary findings with light therapy. Arch Gen Psychiatry 41:72–80
Rothman SM, Mattson MP (2012) Sleep disturbances in Alzheimer’s and Parkinson’s diseases. Neuromol Med 14:194–204
Sae-Ung K, Ueda K, Govitratrapong P, Phansuwan-Pujito P (2012) Melatonin reduces the expression of alpha-synuclein in the dopamine containing neuronal regions of amphetamine-treated postnatal rats. J Pineal Res 52:128–137
Samuel W, Masliah E, Hill LR, Butters N, Terry R (1994) Hippocampal connectivity and Alzheimer’s dementia: effects of synapse loss and tangle frequency in a two-component model. Neurology 44:2081–2088
Savaskan E, Olivieri G, Meier F, Brydon L, Jockers R, Ravid R et al (2002) Increased melatonin 1a-receptor immunoreactivity in the hippocampus of Alzheimer’s disease patients. J Pineal Res 32:59–62
Savaskan E, Ayoub MA, Ravid R, Angeloni D, Fraschini F, Meier F et al (2005) Reduced hippocampal MT2 melatonin receptor expression in Alzheimer’s disease. J Pineal Res 38:10–16
Schenck CH, Montplaisir JY, Frauscher B, Hogl B, Gagnon JF, Postuma R et al (2013) Rapid eye movement sleep behavior disorder: devising controlled active treatment studies for symptomatic and neuroprotective therapy—a consensus statement from the International Rapid Eye Movement Sleep Behavior Disorder Study Group. Sleep Med 14:795–806
Schernhammer ES, Schulmeister K (2004) Melatonin and cancer risk: does light at night compromise physiologic cancer protection by lowering serum melatonin levels? Br J Cancer 90:941–943
Schuster C, Williams LM, Morris A, Morgan PJ, Barrett P (2005) The human MT1 melatonin receptor stimulates cAMP production in the human neuroblastoma cell line SH-SY5Y cells via a calcium-calmodulin signal transduction pathway. J Neuroendocrinol 17:170–178
Selkoe DJ (2004) Cell biology of protein misfolding: the examples of Alzheimer’s and Parkinson’s diseases. Nat Cell Biol 6:1054–1061
Seppi K, Weintraub D, Coelho M, Perez-Lloret S, Fox SH, Katzenschlager R et al (2011) The movement disorder society evidence-based medicine review update: treatments for the non-motor symptoms of Parkinson’s disease. Mov Disord 26(Suppl 3):S42–S80
Serfaty M, Kennell-Webb S, Warner J, Blizard R, Raven P (2002) Double blind randomised placebo controlled trial of low dose melatonin for sleep disorders in dementia. Int J Geriatr Psychiatry 17:1120–1127
Shaikh AY, Xu J, Wu Y, He L, Hsu CY (1997) Melatonin protects bovine cerebral endothelial cells from hyperoxia-induced DNA damage and death. Neurosci Lett 229:193–197
Shen YX, Xu SY, Wei W, Sun XX, Yang J, Liu LH et al (2002) Melatonin reduces memory changes and neural oxidative damage in mice treated with D-galactose. J Pineal Res 32:173–178
Shen Y, Zhang G, Liu L, Xu S (2007) Suppressive effects of melatonin on amyloid-beta-induced glial activation in rat hippocampus. Arch Med Res 38:284–290
Shirazi A, Haddadi GH, Asadi-Amoli F, Sakahae S, Ghazi-Khansari M, Avand A (2011) Radioprotective effect of melatonin in reducing oxidative stress in rat lenses. Cell J 13:79–82
Siegist C, Benedetti C, Orlando A, Beltran JM, Tuchscherer L, Noseda CM et al (2001) Lack of changes in serum prolactin, FSH, TSH, and estradiol after melatonin treatment in doses that improve sleep and reduce benzodiazepine consumption in sleep-disturbed, middle-aged, and elderly patients. J Pineal Res 30:34–42
Silveri MC, Reali G, Jenner C, Puopolo M (2007) Attention and memory in the preclinical stage of dementia. J Geriatr Psychiatry Neurol 20:67–75
Singer C, Tractenberg RE, Kaye J, Schafer K, Gamst A, Grundman M et al (2003) A multicenter, placebo-controlled trial of melatonin for sleep disturbance in Alzheimer’s disease. Sleep 26:893–901
Singh-Manoux A, Dugravit A, Anki J, Nabi H, Ber C, Goldberg M et al (2014) Subjective cognitive complaints and mortality: does the type of complaint matter? J Psychiatr Res 48:73–78
Skene DJ, Swaab DF (2003) Melatonin rhythmicity: effect of age and Alzheimer’s disease. Exp Gerontol 38:199–206
Skene DJ, Vivien-Roels B, Sparks DL, Hunsaker JC, Pevet P, Ravid D et al (1999) Daily variation in the concentration of melatonin and 5-methoxytryptophol in the human pineal gland: effect of age and Alzheimer’s disease. Brain Res 528:170–174
Song W, Lahiri DK (1997) Melatonin alters the metabolism of the beta-amyloid precursor protein in the neuroendocrine cell line PC12. J Mol Neurosci 9:75–92
Spencer JP, Middleton LJ, Davies CH (2010) Investigation into the efficacy of the acetylcholinesterase inhibitor, donepezil, and novel procognitive agents to induce gamma oscillations in rat hippocampal slices. Neuropharmacology 59:437–443
Spuch C, Antequera D, Isabel Fernandez-Bachiller M, Isabel Rodriguez-Franco M, Carro E (2010) A new tacrine-melatonin hybrid reduces amyloid burden and behavioral deficits in a mouse model of Alzheimer’s disease. Neurotox Res 17:421–431
Srinivasan V, Pandi-Perumal SR, Cardinali DP, Poeggeler B, Hardeland R (2006) Melatonin in Alzheimer’s disease and other neurodegenerative disorders. Behav Brain Funct 2:15
Srinivasan V, Kaur C, Pandi-Perumal SR, Brown GM, Cardinali DP (2011a) Melatonin and its agonist ramelteon in Alzheimer’s disease: possible therapeutic value. Int J Alzheimer’s Dis 2011:1–15
Srinivasan V, Cardinali DP, Srinivasan US, Kaur C, Brown GM, Spence DW et al (2011b) Therapeutic potential of melatonin and its analogs in Parkinson’s disease: focus on sleep and neuroprotection. Ther Adv Neurol Disord 14:297–317
Streit WJ, Mrak RE, Griffin WS (2004) Microglia and neuroinflammation: a pathological perspective. J Neuroinflammation 1:14
Struble RG, Cork LC, Whitehouse PJ, Price DL (1982) Cholinergic innervation in neuritic plaques. Science 216:413–415
Stuchbury G, Munch G (2005) Alzheimer’s associated inflammation, potential drug targets and future therapies. J Neural Transm 112:429–453
Subramanian P, Mirunalini S, Pandi-Perumal SR, Trakht I, Cardinali DP (2007) Melatonin treatment improves the antioxidant status and decreases lipid content in brain and liver of rats. Eur J Pharmacol 571:116–119
Tai SH, Hung YC, Lee EJ, Lee AC, Chen TY, Shen CC et al (2011) Melatonin protects against transient focal cerebral ischemia in both reproductively active and estrogen-deficient female rats: the impact of circulating estrogen on its hormetic dose-response. J Pineal Res 50:292–303
Takeuchi N, Uchimura N, Hashizume Y, Mukai M, Etoh Y, Yamamoto K et al (2001) Melatonin therapy for REM sleep behavior disorder. Psychiatry Clin Neurosci 55:267–269
Tan D, Reiter RJ, Chen LD, Poeggeler B, Manchester LC, Barlow-Walden LR (1994) Both physiological and pharmacological levels of melatonin reduce DNA adduction formation induced by the carcinogen safrole. Carcinogenesis 15:215–218
Tan DX, Manchester LC, Terron MP, Flores LJ, Reiter RJ (2007) One molecule, many derivatives: a never-ending interaction of melatonin with reactive oxygen and nitrogen species? J Pineal Res 42:28–42

Tang F, Nag S, Shiu SY, Pang SF (2002) The effects of melatonin and Ginkgo biloba extract on memory loss and choline acetyltransferase activities in the brain of rats infused intracerebroventricularly with beta-amyloid 1-40. Life Sci 71:2625–2631

Tansey MG, McCoy MK, Frank-Cannon TC (2007) Neuroinflammatory mechanisms in Parkinson’s disease: potential environmental triggers, pathways, and targets for early therapeutic intervention. Exp Neurol 208:1–25

Tapia V, Cannon JR, Greenamyre JT (2010) Melatonin treatment potentiates neurodegeneration in a rat rotenone Parkinson’s disease model. J Neurosci Res 88:420–427

Taysi S, Memisogullari R, Koc M, Yazici AT, Aslankurt M, Gumustekin K et al (2008) Melatonin reduces oxidative stress in the rat lens due to radiation-induced oxidative injury. Int J Radiat Biol 84:803–808

Terry AV Jr, Buccafusco JJ (2003) The cholinergic hypothesis of age and Alzheimer’s disease-related cognitive deficits: recent challenges and their implications for novel drug development. J Pharmacol Exp Ther 306:821–827

Thomas B, Mohanakumar KP (2004) Melatonin protects against oxidative stress caused by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine in the mouse nigrostriatum. J Pineal Res 36:25–32

Tsai MC, Chen WJ, Tsai MS, Ching CH, Chuang JJ (2011) Melatonin attenuates brain contusion-induced oxidative insult, inactivation of signal transducers and activators of transcription 1, and upregulation of suppressor of cytokine signaling-3 in rats. J Pineal Res 51:233–245

Urata Y, Honma S, Goto S, Todoroki S, Iida T, Cho S et al (1999) Melatonin induces gamma-glutamylcysteine synthetase mediated by activator protein-1 in human vascular endothelial cells. Free Radic Biol Med 27:838–847

Van Someren EJ (2000) Circadian and sleep disturbances in the elderly. Exp Gerontol 35:1229–1237

Vecchierini MF (2010) Sleep disturbances in Alzheimer’s disease and other dementias. Psychol Neuropsychiat Vieil 8:15–23

Vollrath L, Senn P, Gammel G (1981) Sleep induction by intranasal administration of melatonin. Adv Biosci 29:327–329

Voordouw BC, Euser R, Verdonk RE, Alberda BT, de Jong FH, Drogendijk AC et al (1992) Melatonin and melatonin-progestin combinations alter pituitary-ovarian function in women and can inhibit ovulation. J Clin Endocrinol Metab 74:108–117

Wade AG, Ford I, Crawford G, McMahon AD, Nir T, Laudon M et al (2007) Efficacy of prolonged release melatonin in insomnia patients aged 55–80 years: quality of sleep and next-day alertness outcomes. Curr Med Res Opin 23:2597–2605

Waldhauser F, Waldhauser M, Lieberman HR, Deng MH, Lynch HJ, Wurtman RJ (1984) Bioavailability of oral melatonin in humans. Neuroendocrinology 39:307–313

Waldhauser F, Saletu B, Trinchard-Lugan I (1990) Sleep laboratory investigations on hypnotic properties of melatonin. Psychopharmacol (Berl) 100:222–226

Wang YP, Li XT, Liu SJ, Zhou XW, Wang XC, Wang JZ (2004) Melatonin ameliorated okadaic-acid induced Alzheimer-like lesions. Acta Pharmacol Sin 25:276–280

Wang XC, Zhang J, Yu X, Han L, Zhou ZT, Zhang Y et al (2005) Prevention of isoproterenol-induced tau hyperphosphorylation by melatonin in the rat. Sheng Li Xue Bao 57:7–12

Weishaupt JH, Bartels C, Polking E, Dietrich J, Rohde G, Poeggeler B et al (2006) Reduced oxidative damage in ALS by high-dose enteral melatonin treatment. J Pineal Res 41:313–323

Weidemichael DA, Grossberg GT (2010) Circadian rhythm disturbances in patients with Alzheimer’s disease: a review. Int J Alzheimer’s Dis 2010. doi:10.4061/2010/716453

Weberne U, Turner T, Priebel S (2006) Complementary medicines in psychiatry: review of efficacy and safety. Br J Psychiatry 188:109–121
Wiesenber I, Missbach M, Kahlen JP, Schrader M, Carlberg C (1995) Transcriptional activation of the nuclear receptor RZR alpha by the pineal gland hormone melatonin and identification of CGP 52608 as a synthetic ligand. Nucleic Acids Res 23:327–333
Willis GL (2008) Parkinson’s disease as a neuroendocrine disorder of circadian function: dopamine-melatonin imbalance and the visual system in the genesis and progression of the degenerative process. Rev Neurosci 19:245–316
Willis GL, Armstrong SM (1999) A therapeutic role for melatonin antagonism in experimental models of Parkinson’s disease. Physiol Behav 66:785–795
Willis GL, Robertson AD (2004) Recovery of experimental Parkinson’s disease with the melatonin analogues ML-23 and S-20928 in a chronic, bilateral 6-OHDA model: a new mechanism involving antagonism of the melatonin receptor. Pharmacol Biochem Behav 79:413–429
Willis GL, Turner EJ (2007) Primary and secondary features of Parkinson’s disease improve with strategic exposure to bright light: a case series study. Chronobiol Int 24:521–537
Wilson SJ, Nutt DJ, Alford C, Argyropoulos SV, Baldwin DS, Bateson AN et al (2010) British Association for Psychopharmacology consensus statement on evidence-based treatment of insomnia, parasomnias and circadian rhythm disorders. J Psychopharmacol 24:1577–1601
Witt-Enderyby PA, MacKenzie RS, McKeon RM, Carroll EA, Bordt SL, Melan MA (2000) Melatonin induction of filamentous structures in non-neuronal cells that is dependent on expression of the human mt1 melatonin receptor. Cell Motil Cytoskeleton 46:28–42
Wu YH, Swaab DF (2007) Disturbance and strategies for reactivation of the circadian rhythm system in aging and Alzheimer’s disease. Sleep Med 8:623–636
Wu YH, Feenstra MG, Zhou JN, Liu YR, Torano JS, Van Kan HJ et al (2003) Molecular changes underlying reduced pineal melatonin levels in Alzheimer disease: alterations in preclinical and clinical stages. J Clin Endocrinol Metab 88:5898–5906
Wu YH, Zhou JN, Van Heerikhuize J, Jockers R, Swaab DF (2007) Decreased MT1 melatonin receptor expression in the suprachiasmatic nucleus in aging and Alzheimer’s disease. Neurobiol Aging 28:1239–1247
Xiong YF, Chen Q, Chen J, Zhou J, Wang HX (2011) Melatonin reduces the impairment of axonal transport and axonopathy induced by calyculin A. J Pineal Res 50:319–327
Zatta P, Tognon G, Carampin P (2003) Melatonin prevents free radical formation due to the interaction between beta-amyloid peptides and metal ions [Al115, Zn11, Cu11, Mn11, Fe21]. J Pineal Res 35:98–103
Zhang Y, Dawson VL, Dawson TM (2000) Oxidative stress and genetics in the pathogenesis of Parkinson’s disease. Neurobiol Dis 7:240–250
Zhang YC, Wang ZF, Wang Q, Wang YP, Wang JZ (2004) Melatonin attenuates beta-amyloid-induced inhibition of neurofilament expression. Acta Pharmacol Sin 25:447–451
Zhphanova IV, Wurtman RJ, Regan MM, Taylor JA, Shi JP, Leclair OU (2001) Melatonin treatment for age-related insomnia. J Clin Endocrinol Metab 86:4727–4730
Zhou JN, Liu YR, Kamphorst W, Hofman MA, Swaab DF (2003) Early neuropathological Alzheimer’s changes in aged individuals are accompanied by decreased cerebrospinal fluid melatonin levels. J Pineal Res 35:125–130
Zhu LQ, Wang SH, Ling ZQ, Wang DL, Wang JZ (2004) Effect of inhibiting melatonin biosynthesis on spatial memory retention and tau phosphorylation in rat. J Pineal Res 37:71–77