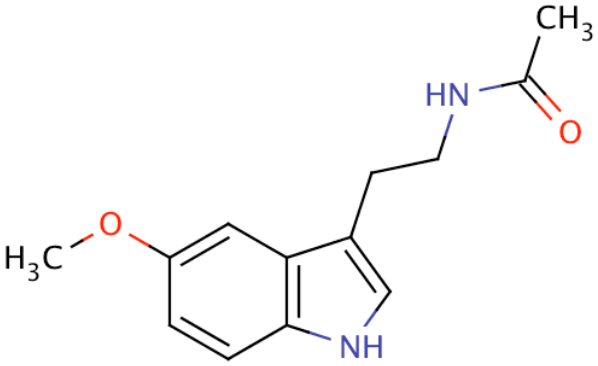
CINAPS Compound Dossier

Melatonin



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National Institute of Neurological Disorders and Stroke

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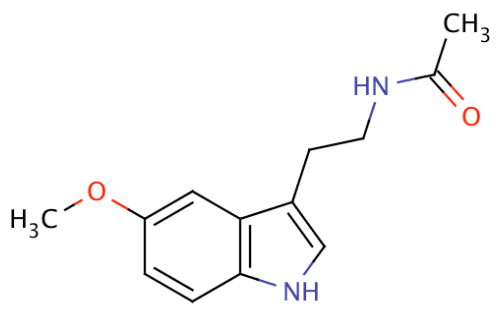
I. Compound Information

Common name	Melatonin
Structure	

PubChem ID	896	**MF**	C13 H16 N2 O2	**MW**	232.28
CASRN	73-31-4	**Polar surface area**	50.36	**logP**	0.48

IUPAC name	N-[2-(5-methoxy-1H-indol-3-yl)ethyl]acetamide
Other names	N-Acetyl-5-methoxytryptamine; 5-Methoxy-N-acetyltryptamine
Drug class	Antioxidant
Notes	
Development status	Marketed in the U.S. as an over-the-counter drug and dietary supplement.

II. Rationale

IIa. Scientific Rationale / Mechanism

Oxidative stress and generation of free radicals from both mitochondrial impairment and dopamine metabolism are considered to play critical roles in Parkinson's Disease (PD) etiology. Thus, the use of antioxidants as an important co-treatment with traditional therapies for PD has been suggested. Melatonin (N-acetyl-5-methoxy-tryptamine), an endogenous pineal hormone associated with the maintenance of diurnal rhythms, has been shown to have potent endogenous antioxidant actions. Because neurodegenerative disorders are mainly caused by oxidative damage, melatonin has been tested successfully in both in vivo and in vitro models of PD (**Mayo, 2005**).

Melatonin has been shown to be one of the best physiological antioxidants and in vivo cell protectors Melatonin is distinguished by its solubility in both lipids and water and by its ability to pass the blood/brain barrier allowing access to both glial and neuronal cells (**Antolin, 2002**).

Melatonin prevents 6-hydroxydopamine induced apoptosis in naïve and neuronal PC12 cells (**Mayo, 1998**).

Low (100nM) and high (1mM) dose melatonin protects cultured rat astrocytes from oxidative stress (**Martin, 2002**).

Primary rat neurons were grown in low density in serum-free media. Under these conditions, nearly all cells died, presumably due to the lack of essential growth factors. Treatment with 250 µM melatonin rescued nearly all dying cells (100% tau+ neurons), including tyrosine hydroxylase immunopositive DA neurons, for at least 7 days following growth factor deprivation. This effect was dose and time dependent and was mimicked by other antioxidants such as 2-iodomelatonin and vitamin E. Similarly, in the second model of oxidative stress, 250 µM melatonn produced a near total recovery from the usual 50% loss of dopamine (DA) neurons caused by neurotoxic injury from 2.5 µM 1-methyl-4-phenylpyridine (MPP+) (**Iacovitti, 1997**).

A reduction by melatonin in nigrostriatal dopaminergic activity could theoretically lead to worsening of parkinsonian symptoms, as is indeed suggested by findings in animal models of PD (**Willis, 1999**). Therefore, melatonin may be beneficial for neuroprotection against further loss of striatal neurons but may potentially exacerbate motor dysfunction in patients who have already developed the disease (**Zisapel, 2001**).

IIb. Consistency

Melatonin (10mg/kg) did not protect against MPTP-induced neurotoxicity in Swiss Webster mice although it did protect against methamphetamine administration (**Itzhak, 1998**),

III. Efficacy (animal models of Parkinson's disease)

IIIa. Animal Models: Rodent

C57/Bl6 mice were treated with MPTP (15 mg/kg) and 24 h later DA turnover, tyrosine hydroxylase activity, lipid peroxidation and mitochondrial complex I activity were determined in nigrostriatal tissue. Locomotor activity was also measured before and after MPTP treatment. To study the neuroprotective effects of melatonin and deprenyl, the drugs were administered alone or in combination 30 min before the neurotoxin, followed by the same determinations 24 h later. Melatonin (10 mg/kg), but not deprenyl (0.37 mg/kg) prevents the inhibition of mitochondrial complex I and the oxidative damage in nigrostriatal neurons induced by MPTP. With the dose used deprenyl recovers 50% DA levels and tyrosine hydroxylase activity depressed by the neurotoxin, normalizing locomotor activity of mice. Although melatonin was unable to counteract MPTP-induced DA depletion and inhibition of tyrosine hydroxylase activity, it does potentiate the effect of deprenyl on catecholamine turnover and mice ambulatory activity. These results suggest a dissociation of complex I inhibition from DA depletion in this model of Parkinson's disease. The data also support that a combination of melatonin, which improves mitochondrial electron transport chain and reduces oxidative damage, and deprenyl, which promotes the specific function of the rescued neurons, i.e. DA turnover, may be a promising strategy for the treatment of PD (**Khaldy, 2003**).

Co-administration of melatonin (5.0 mg/kg, i.p., twice in a 12-h interval) with L-DOPA, in control as well as in light-exposed rats, significantly increased dialysate L-DOPA concentrations, greatly inhibited L-DOPA semiquinone formation, and restored up to the control values dialysate DA and ascorbic acid concentrations. These findings demonstrate that endogenous melatonin protects exogenous L-DOPA from autoxidation in the extracellular compartment of the striatum of freely moving rats; moreover, systemic co-administration of melatonin with L-DOPA markedly increases striatal L-DOPA bioavailability in control as well as in melatonin-depleted rats. These results may be of relevance to the long-term L-DOPA therapy of Parkinson's disease (**Rocchitta, 2006**).

Rotenone subcutaneously infused for 14 days induced PD symptoms in rats indicated by reduced spontaneous locomotor activity, loss of tyrosine hydroxylase immunoreactivity in the substantis nigra and striatum, obvious α-synuclein accumulation, downregulated DAT protein expression and upregulated D2R expression. Co-administration of melatonin prevented nigrostriatal neurodegeneration and α-synuclein aggregation without affecting the rotenone-induced weight loss and hypokinesis (**Lin, 2008**).

Chronic melatonin administration following unilateral intranigral infusion of rotenone in rats reduced the rotenone-induced increase in hydroxyl radicals and prevented the reduction in activity of antioxidant enzymes glutathione, superoxide dismutase, and catalase (**Saravanan, 2007**).

MPTP-treated mice do not show any loss of or damage to nigral cells when simultaneously given melatonin (500 µg/kg bw) (**Antolin, 2002**).

At 2 weeks after partial 6-hydroxydopamine lesioning in the striatum rats chronically treated with melatonin via drinking water exhibited significantly attenuated rotational behavior. After 10 weeks animals treated with 4.0 µg/ml melatonin exhibited normal tyrosine hydroxylase (TH) immunoreactivity in the lesioned striatum. These findings support a physiological role for melatonin in protecting against parkinsonian neurodegeneration in the nigrostriatal system (**Sharma, 2006**).

IIIb. Animal Models: Non-human primates

ML-23, a melatonin receptor antagonist, or possible partial agonist, was administered orally in a dose of 3 mg/kg twice daily for 56 days in the MPTP PD model in the common marmoset. ML-23 produced a significant remission (which persisted after the withdrawal of the drug) from MPTP-induced Parkinsonism. (**Willis, 2005**)

IV. Efficacy (Clinical and Epidemiological Evidence)

IVa. Clinical studies

Melatonin did not ameliorate parkinson's disease symptoms in human patients (**Shaw, 1973**; **Papavasiliou, 1972**). In the Shaw, et al. study melatonin, in doses up to 1 gram/day, was administered to four parkinsonian patients for four weeks.

The effect of melatonin on sleep and motor dysfuntion in PD were studied in a group of 18 patients from a PD clinic. Although melatonin significantly improved subjective quality of sleep evaluated by the Pittsburgh Sleep Quality Index (PSQI), polysomnography (PSG) abnormalities were not changed. Motor dysfunction was not improved by the use of melatonin (**Medeiros, 2007**).

IVb. Epidemiological evidence

With regards to epidemiological evidence which may arise from the use of melatonin it should be noted that there is potential for widespread human subject exposure to synthetic melatonin available as a drug. It is inexpensive and readily available over the counter in drug stores, health food stores, and supermarkets as a health and nutrition supplement. Several subpopulations have been identified as likely to be exposed to melatonin used to adjust circadian rhythms (**Dawson, 1995**). Ubeda, et al. reported that pharmacological levels of melatonin occur in a concentration range of 10^{-9} to 10^{-8} m/L. There is, of course, the possibility that a percentage of melatonin consumers will engage in excessive self-administration (**Ubeda, 1995**).

V. Relevance to other neurodegenerative diseases

Melatonin is neuroprotective in experimental models of stroke in rats (reviewed in **MacLeod, 2005**).

VI. Pharmacokinetics

VIa. General ADME

In healthy adults, normal plasma levels of melatonin average less than 10 pg/mL during the daylight hours. Around 10 p.m., levels begin to rise, reaching an average of 90 pg/mL between 2 and 4 a.m. There is substantial intersubject variability in both daytime and night time plasma melatonin levels. Normal endogenous production of melatonin is estimated to be 28-30 μg/day.

Also in healthy adults, melatonin is rapidly absorbed after oral administration, with peak plasma levels occurring in 0.5 to 2 hours. The bioavailability of immediate-release oral doses ranges from 3% to 76% and is not significantly affected by food. Hepatic first-pass metabolism of an oral dose is substantial (as much as 60%). The volume of distribution is approximately 35 L, and elimination half-life is 30-50 minutes. Exogenously administered melatonin is metabolized by CYP1A2 to the inactive metabolites 6-hydroxymelatonin (approximately 85%) and N-acetylserotonin (approximately 15%), which are subsequently excreted in the urine. Oral transmucosal (sublingual) dosage forms, taken before bedtime, appear to more closely mimic endogenous nocturnal output of melatonin (**Pepping, 1999**).

VIb. CNS Penetration

"The blood-brain barrier is no impediment to the passage of melatonin into the brain." (**Reiter, 1991**)

VIc. Calculated logBB (Clark Model) -0.53

VII. Safety, Tolerability, and Drug Interaction Potential

VIIa. Safety and Tolerability

Sedation, drowsiness, and mild hypothermia (0.5-1.5 °F) are the most common adverse effects of melatonin in therapeutic dosages. Other reported adverse effects include altered sleep patterns, increased seizure activity in neurologically impaired pediatric patients, fatigue, headache, confusion, pruritus, dysphoria, and one case of possible autoimmune hepatitis (**Pepping, 1999**).

VIIb. Drug Interaction Potential

Clearance of melatonin is delayed in patients concurrently taking chlorpromazine. In mice, long-term benzodiazepine administration lowers nocturnal secretion of melatonin; in addition, melatonin is thought to enhance the anxiolytic action of benzodiazepines by increasing binding of benzodiazepines to CNS receptor sites. Recent murine studies have shown that tolerance of and dependence on morphine were reversed by intraperitoneally administered melatonin (**Pepping, 1999**).

Melatonin is contraindicated in multiple sclerosis and other autoimmune diseases because of its potential to exacerbate these conditions. Caution should be used in patients with depression (dysphoric reactions have been reported), seizures, and other neurologic disorders (melatonin is a proconvulsant in neurologically disabled pediatric patients). Melatonin may have increased pharmacologic effects in patients with hepatic insufficiency because of reduced clearance (**Pepping, 1999**).

Melatonin increases the activity of antioxidant enzymes and their gene expression (reviewed in **Rodriguez, 2004**).

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