

Melatonin Receptors

Key References

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Overview

The hormone melatonin is produced primarily in the mammalian pineal gland and retina following a circadian rhythm with high levels being released at night. The circadian secretion of melatonin is controlled by the master biological clock located within the suprachiasmatic nucleus of the hypothalamus and synchronized to a 24 hour cycle by the daily photoperiod. In mammals, melatonin has been implicated in the regulation of sleep, circadian rhythms, retina physiology, cardiovascular and immune function and cancer cell growth. These effects of melatonin appear to be mediated, at least in part, through activation of high affinity G protein-coupled melatonin receptors. However, an action of melatonin as a ligand for putative nuclear melatonin receptors, as a calmodulin antagonist, inhibitor of NO production, scavenger of free radicals and an antioxidant cannot be excluded at the present time.

Membrane-associated melatonin receptors were originally classified based on kinetic properties and pharmacological profiles into the ML₁ and ML₂ classes with 2-[¹²⁵I]-iodomelatonin binding affinities in the picomolar and nanomolar range, respectively. cDNA's encoding melatonin receptors with the ML₁-like pharmacology profile (i.e., 2-iodomelatonin > melatonin > 6-chloromelatonin > N-acetylserotonin >> serotonin) were cloned (Mel_{1a}, Mel_{1b}, Mel_{1c}) in several vertebrate species including humans. These receptors are coupled to pertussis toxin-sensitive G proteins, and are members of a new subfamily of G protein-coupled receptors. The mammalian melatonin receptors are now referred as MT₁ (formerly Mel_{1a}) and MT₂ (formerly Mel_{1b}). The MT₁ and MT₂ melatonin receptors exhibiting 60% amino acid homology, show different molecular structure, distinct

chromosomal localization and pharmacological profile. The Mel_{1c}, originally cloned from *Xenopus laevis* melanophores, is not found in mammals.

The competitive melatonin receptor antagonists luzindole and S 20928 as well as MT₂ selective melatonin receptor antagonists (e.g. 4P-ADOT and 4P-PDOT) allowed identification of several functional responses for melatonin. The presynaptic melatonin receptor modulating dopamine release from retina shows the pharmacology of the MT₂ melatonin receptor. In the rat suprachiasmatic nucleus slice preparation, activation of the MT₁ receptor inhibits neuronal firing while activation of the MT₂ melatonin receptor phase shifts the peak of circadian rhythm of neuronal activity. Melatonin appears to mediate dual responses in mammalian arteries possible through activation of the MT₁ (e.g., vasoconstriction) and MT₂ (i.e., vasodilation) melatonin receptors.

The putative MT₃ (formerly ML₂) type of melatonin receptor binds 2-[¹²⁵I]-iodomelatonin with nanomolar affinity, displays a distinct pharmacological profile (i.e., 2-iodomelatonin > 6-chloromelatonin > N-acetylserotonin > melatonin >> serotonin), and is coupled to the stimulation of phosphoinositide turnover. This binding site was originally thought to be a G protein-coupled receptor; however, recently a protein from hamster kidney, subsequently identified as quinone reductase II, was found to bind 2-[¹²⁵I]-iodomelatonin while demonstrating the same pharmacology as the putative MT₃ melatonin receptor site. Specific 2-[¹²⁵I]-iodomelatonin binding to MT₃ binding sites were absent in brain and kidney membranes from mice with genetic deletion of quinone reductase 2. The physiological

responses associated with these putative MT₃ sites are not known.

Together the use of melatonin receptor specific and receptor selective analogs is essential to unravel the signaling pathways and the associated neuroendocrine and functional responses to melatonin in mammals. The use of MT₁, MT₂ and MT₃ melatonin receptor agonists and antagonists will help to further elucidate the mechanism(s) of melatonin's action in mammals and may prompt the development of selective analogs for the treatment of insomnia and circadian sleep and mood disorders.

Melatonin Receptors

CURRENTLY ACCEPTED NAME	MT ₁	MT ₂	MT ₃
PREVIOUS NAMES	Mel _{1a} ML _{1A} MEL _{1A}	Mel _{1b} ML _{1B} MEL _{1B}	ML ₂
STRUCTURAL INFORMATION	350 aa (human)	363 aa (human)	Not known
FULL AGONISTS	Melatonin (M5250), 2-Iodomelatonin (I1899), N-Propionyl melatonin, N-Butanoyl melatonin, 6-Chloromelatonin (C0331), 2-Methyl-6,7-dichloromelatonin, S20098, GR 196429, 8M-PDOT, (-)-AMMTC, S26131	Melatonin (M5250), 2-Iodomelatonin (I1899), N-Propionyl melatonin, N-Butanoyl melatonin, 6-Chloromelatonin (C0331), 2-Methyl-6,7-dichloromelatonin, S20098, GR 196429, 8M-PDOT, (-)-AMMTC, IIK7 (I5531)	2-Iodomelatonin (I1899), 6-Chloromelatonin (C0331), Melatonin (M5250), N-Acetylserotonin (A1824), 5-MCA-NAT (G0294)
PARTIAL AGONISTS	5-Methoxyluzindole, N-Acetyltryptamine (A7342)	5-Methoxyluzindole, N-Acetyltryptamine (A7342)	Not known
ANTAGONISTS	Luzindole (L2407), S20928	Luzindole (L2407), S20928, 4P-PDOT, 4P-ADOT, K185 (K1888)	Luzindole (L2407), Prazosin (P7791) Prazosin (P7791)
SIGNAL TRANSDUCTION MECHANISMS	G _i (cAMP modulation) G _{q/11} (increase IP ₃ /DAG)	G _i (cAMP modulation) cGMP modulation	G _{q/11} (increase IP ₃ /DAG)
RADIOLIGANDS OF CHOICE	2-[¹²⁵ I]-Iodomelatonin [³ H]-Melatonin	2-[¹²⁵ I]-Iodomelatonin [³ H]-Melatonin	2-[¹²⁵ I]-Iodomelatonin 2-[¹²⁵ I]-MCA-NAT
TISSUE EXPRESSION	Suprachiasmatic nucleus, retina, cerebellum, arteries, pars tuberalis	Suprachiasmatic nucleus, retina, cerebellum, arteries	Brain, kidney, testis
PHYSIOLOGICAL FUNCTION	Inhibition neuronal firing, inhibition prolactin secretion, vasoconstriction	Phase shift circadian rhythms, of neuronal firing, inhibition, dopamine release, vasodilation	Not known
DISEASE RELEVANCE	Insomnia	Phase shift circadian rhythms, increase immune function	Decrease intraocular pressure

Abbreviations

4P-ADOT: 4-Phenyl-2-acetamidotetralin

(-)-AMMTC: N-Acetyl-4-aminomethyl-6-methoxy-9-methyl-1,2,3,4-tetrahydrocarbazole

4P-CADOT: 4-Phenyl-2-chloroacetamidotetralin

GR 196429: N-[2-[2,3,7,8-Tetrahydro-1H-furo[2,3-g]indol-1-yl]ethyl]acetamide

IIK7: N-Butanoyl-2-(2-methoxy-6H-isoindolo[2,1-a]indole-11-yl)ethanamine

K185: N-Butanoyl-2-(5,6,7-trihydro-11-methoxybenzo[3,4]cyclohept[2,1-a]indol-13-yl)ethanamine

Luzindole: 2-Benzyl-N-acetyltryptamine

5-MCA-NAT: 5-Methoxycarbonylamino-N-acetyltryptamine

Melatonin: 5-Methoxy-N-acetyltryptamine

4P-PDOT: 4-Phenyl-2-propionamidotetralin

8M-PDOT: 8-Methoxy-2-propionamidotetralin

S20098: N-[2-(7-Methoxy-1-naphthalenyl)ethyl]acetamide

S20928: N-[2-Naphth-1-yl-ethyl]-cyclobutyl carboxamide

S26131: N-(2-[7-3-((8-[2-Acetylamino]ethyl)-2-naphthyl)oxy]propoxy)-1-naphthyl)ethyl]acetamide

FOOTNOTES