



Minireview

Melatonin: A hormone that modulates pain

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ABSTRACT

Aims: Melatonin is a hormone synthesized principally in the pineal gland that has been classically associated with endocrine actions. However, several lines of evidence suggest that melatonin plays a role in pain modulation. This paper reviews the available evidence on melatonin's analgesic effects in animals and human beings.

Main methods: A medline search was performed using the terms “melatonin”, “inflammatory pain”, “neuropathic pain”, “functional pain”, “rats”, “mice”, “human”, “receptors”, “opioid” and “free radicals” in combinations.

Key findings: The antinociceptive effect of melatonin has been evaluated in diverse pain models, and several findings show that melatonin receptors modulate pain mechanisms as activation induces an antinociceptive effect at spinal and supraspinal levels under conditions of acute and inflammatory pain. More recently, melatonin induced-antinociception has been extended to neuropathic pain states. This effect agrees with the localization of melatonin receptors in thalamus, hypothalamus, dorsal horn of the spinal cord, spinal trigeminal tract, and trigeminal nucleus. The effects of melatonin result from activation of MT₁ and MT₂ melatonin receptors, which leads to reduced cyclic AMP formation and reduced nociception. In addition, melatonin is able to activate opioid receptors indirectly, to open several K⁺ channels and to inhibit expression of 5-lipoxygenase and cyclooxygenase 2. This hormone also inhibits the production of pro-inflammatory cytokines, modulates GABA_A receptor function and acts as a free radical scavenger.

Significance: Melatonin receptors constitute attractive targets for developing analgesic drugs, and their activation may prove to be a useful strategy to generate analgesics with a novel mechanism of action.

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Introduction

Melatonin (N-acetyl-5-methoxytryptamine, Fig. 1) is a hormone mainly produced by the pineal gland in all vertebrates and follows a circadian pattern. Melatonin was initially studied in terms of its role in endocrine physiology regulating circadian and, sometimes, seasonal rhythms (Vanecek 1998). However, evidence has been accumulated showing that melatonin influences the function of a variety of tissues not related to the endocrine system (Vanecek 1998) and that it can play an important role in pain regulation. It has been suggested that melatonin exerts its actions *via*: (i) a membrane-signaling pathway, (ii) a nuclear signaling pathway and (iii) a receptor-independent radical scavenging function. The potential relevance of melatonin to pain is emphasized by its widespread presence in the central nervous system (CNS). The aim of this review is to analyze different lines of evidence for the role of melatonin in different pain states as well as to describe the profile of melatonin as a potential analgesic.

Synthesis

Melatonin's circadian secretion is controlled by the hypothalamic suprachiasmatic nucleus, with the higher levels produced at night (Vanecek 1998). Melatonin is synthesized from serotonin by a two-step pathway involving N-acetylation and O-methylation. The first step is catalyzed by the enzyme arylalkylamine N-acetyltransferase (NAT) and the second one, by the hydroxyindole-O-methyltransferase enzyme. In mammalian pineal gland, noradrenergic fibers originating from the superior cervical ganglia control melatonin day/night synthesis and release. Noradrenaline released at night binds to post-synaptic adrenoceptors whose activation induces an increase in cyclic adenosine-3',5'-monophosphate (cyclic AMP) accumulation and a subsequent activation of NAT (Sugden 1989). N-acetylation of serotonin is the rate-limiting factor in melatonin formation. In vertebrates, melatonin is mainly synthesized in the pineal gland, but other organs and cells, including the retina, skin and gastrointestinal tract (Vanecek 1998) can contribute, although poorly, to circulating melatonin upon specific stimuli.

Melatonin has two important functional groups which determine its specificity and amphiphilicity: the 5-methoxy group and the N-acetyl side chain. Due to its lipophilic nature and pKa, melatonin readily crosses the blood–brain barrier. Once synthesized, the majority of melatonin diffuses directly towards the cerebrospinal fluid of the brain's third ventricle, while another fraction is released into the blood stream where it is distributed to all tissues (Reppert et al. 1979). Circulating melatonin is metabolized by P-450 liver enzymes, which hydroxylate this hormone at the 6-carbon position to yield 6-hydroxymelatonin. This reaction is followed by conjugation with sulfuric or glucuronic acid, to produce the principal urinary metabolite, 6-sulfatoxymelatonin. In the last step, conjugated melatonin and minute quantities of unmetabolized melatonin are eliminated

through the kidney. In addition to hepatic metabolism, oxidative pyrrole-ring cleavage appears to be the major metabolic pathway in other tissues, including the CNS (Hirata et al. 1974).

Melatonin receptors and transduction systems

Melatonin binding sites with distinct pharmacological profiles have been cloned and characterized in a great number of tissues (Morgan et al. 1994; Dubocovich and Markowska 2005). It is widely accepted that some important effects of melatonin are mediated through activation of high affinity G-protein coupled specific receptors. The distribution and pharmacological properties of melatonin receptors have been discussed previously (Morgan et al. 1994; Vanecek 1998; Browning et al. 2000), so only a brief reference will be given here with an emphasis on nociception related aspects.

Melatonin exhibits high affinity binding to its receptors, of less than 500 pM (Sugden et al. 2004). There are four different melatonin receptor subtypes. Two of them are membrane-associated receptors, while the other two are nuclear receptors. Membrane melatonin receptors are classified based upon their kinetic properties and pharmacological profiles into MT₁ (Mel 1a) and MT₂ (Mel 1b) melatonin receptor subtypes (Dubocovich and Markowska 2005). They belong to the seven transmembrane receptor family, have 60% aminoacid homology, and differ in molecular structure and gene chromosomal localization (Reppert et al. 1997). MT₁ and MT₂ melatonin receptor subtypes are present in humans and other mammals (Reppert et al. 1997). The MT₂ melatonin receptor has lower affinity (K_d = 160 pmol/l) for ¹²⁵I-melatonin as compared to the human MT₁ melatonin receptor (K_d = 20–40 pmol/l) (Dubocovich and Markowska 2005). Although several authors proposed the existence of a putative MT₃ melatonin receptor subtype, recent studies have provided evidence that the MT₃ melatonin receptor is actually a cytosolic quinone reductase 2 enzyme rather than a membrane receptor (Mailliet et al. 2005). For this reason, the MT₃ melatonin receptor subtype is no longer recognized in IUPHAR's classification as a G protein-coupled melatonin receptor subtype (<http://www.iuphar-db.org/iuphar-rd>).

Melatonin is also a ligand for retinoid orphan nuclear hormone receptors (Becker-Andre et al. 1994), referred to as RZR α and RZR β at concentrations in the low nanomolar range. Both receptors are present in the central and peripheral nervous system and have been associated with cell differentiation and immune response regulation (Smirnov 2001). *In situ* hybridization experiments have demonstrated mRNA expression of the RZR β melatonin receptors in the rat brain and neurons of several sensory regions including the dorsal horn of the spinal cord, but not in regions involved in motor control (Park et al. 1997). These results suggest that RZR β plays a specific role as a transcription factor in the sensory system. On the other hand, the RZR α melatonin receptor has been implicated in inflammatory reactions. Thus, Steinhilber et al. (1995) reported that melatonin can down-regulate the expression of 5-lipoxygenase (5-LOX), an important inflammatory mediator, in B lymphocytes *via* RZR α receptors. Even though details on the targets are still unknown, one cannot exclude the possibility that some melatonin actions on pain modulation are mediated through nuclear receptors.

As previously mentioned, melatonin's antinociceptive and anti-inflammatory effects are mainly mediated through specific membrane associated-receptors negatively coupled to adenylyl cyclase. This has been described in several experimental preparations. For example, in Chinese hamster ovary cells expressing MT₁ and MT₂ melatonin receptors, melatonin inhibits forskolin-stimulated accumulation of cyclic AMP (Browning et al. 2000); this response was abolished by pertussis toxin indicating that Gi/Go protein activation is involved (Browning et al. 2000). Melatonin receptor activation also increases cyclic guanosine monophosphate (cyclic GMP). Other mediators such as Ca²⁺, diacylglycerol, inositol

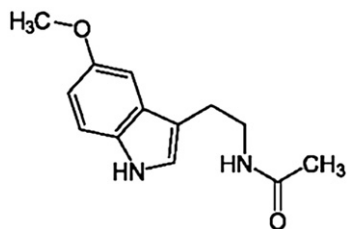


Fig. 1. Chemical structure of melatonin.

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