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Review

Potential use of melatonergic drugs in analgesia: Mechanisms of action

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ABSTRACT

Melatonin is a remarkable molecule with diverse physiological functions. Some of its effects are mediated by receptors while other, like cytoprotection, seem to depend on direct and indirect scavenging of free radicals not involving receptors. Among melatonin's many effects, its antinociceptive actions have attracted attention. When given orally, intraperitoneally, locally, intrathecally or through intracerebroventricular routes, melatonin exerts antinociceptive and antiallodynic actions in a variety of animal models. These effects have been demonstrated in animal models of acute pain like the tail-flick test, formalin test or endotoxin-induced hyperalgesia as well as in models of neuropathic pain like nerve ligation. Glutamate, gamma-aminobutyric acid, and particularly, opioid neurotransmission have been demonstrated to be involved in melatonin's analgesia. Results using melatonin receptor antagonists support the participation of melatonin receptors in melatonin's analgesia. However, discrepancies between the affinity of the receptors and the very high doses of melatonin needed to cause effects in vivo raise doubts about the uniqueness of that physiopathological interpretation. Indeed, melatonin could play a role in pain through several alternative mechanisms including free radicals scavenging or nitric oxide synthase inhibition. The use of melatonin analogs like the MT_1/MT_2 agonist ramelteon, which lacks free radical scavenging activity, could be useful to unravel the mechanism of action of melatonin in analgesia. Melatonin has a promising role as an analgesic drug that could be used for alleviating pain associated with cancer, headache or surgical procedures.

Contents

1. Introduction

Melatonin (*N*-acetyl-5-methoxytryptamine) has been characterized as a remarkable molecule with diverse physiological functions, including the control of circadian rhythms [6,78], sleep regulation [17], enhancement of immunological functioning

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[22,84], free radical scavenging and antioxidant effects [119,139], inhibition of oncogenesis [15,134], mood regulation [106], vasoregulation [35] and regulation of seasonal reproductive activity [80,121]. Among that broad range of effects attributed to melatonin, its role in analgesia emerges as important because of its clinical implications.

Several early studies in mice [16,29,68,73], hamsters [114], rats [11,92,115,125] and man [33] showed that there is a circadian rhythm in pain perception. Furthermore, the pain threshold rhythm as measured by the tail-flick test or by the hot-plate test is abolished in the rat either by functional pinealectomy by light [11,12,66] or by surgical pinealectomy [11]. Oral melatonin replacement in a physiological dosage reproducing the baseline 24 h rhythm of 6-sulphatoxymelatonin output restored the rhythm in both pressure-induced and heat-produced nociception that is abolished by light suppression [65,66]. Thus there is evidence that there is a physiologic antinociceptive effect of melatonin driving a circadian rhythm in pain perception. The antinociceptive effect of pharmacological doses of melatonin has therefore been examined in several animal models of pain perception (Table 1).

The pain modulatory role of melatonin has been also explored in human subjects [19,23–25,46,54,63,89,94,97,100,109,112,113,118,135]. The purpose of this review is to discuss the pharmacological basis for the antinociceptive role of melatonin and its analogs and the possible mechanisms by which they cause analgesia. For a recent review on the modulatory role of melatonin in pain see [5].

2. Melatonin biosynthesis, metabolism and receptors

In all mammals circulating melatonin is synthesized primarily in the pineal gland [26]. In addition, melatonin is also locally synthesized in various cells, tissues and organs including lymphocytes [20], human and murine bone marrow [28], the thymus [101], the gastrointestinal tract [18], skin [133] and, except in humans and rhesus monkeys, in the eyes [83]. In these tissues melatonin seems to plays either an autocrine or paracrine role.

Tryptophan serves as the precursor for the biosynthesis of melatonin [1]. It is taken up from the blood and is converted into serotonin via 5-hydroxytryptophan. Serotonin is then acetylated to form *N*-acetylserotonin through the action of arylalkylamine *N*-acetyltransferase (AANAT), one of the key enzymes in melatonin synthesis. *N*-acetylserotonin is then converted to melatonin by hydroxyindole-O-methyltransferase, which has been identified as a rate-limiting enzyme in the biosynthesis of melatonin [1].

Pineal melatonin biosynthesis is regulated by the light–dark cycle via the retinohypothalamic tract [95]. Special melanopsin-containing retinal ganglion cells [13] project to the suprachiasmatic nucleus of the hypothalamus. Other neuronal circuits include the hypothalamic paraventricular nucleus, the medial forebrain bundle and the reticular formation to influence intermediolateral horn cells of the spinal cord, which are the preganglionic neurons that innervate the superior cervical ganglion (SCG) [96]. The postganglionic fibers that arise from SCG regulate pineal melatonin biosynthesis by releasing norepinephrine (NE) at its pinealocyte receptor sites. NE, by interacting mainly with β_1-, but also with α_1-adrenergic receptors in the pineal gland, activates the adenylyl cyclase-cyclic AMP pathway which in turn regulates expression of enzymes in melatonin biosynthetic pathway [1]. α_1-Adrenergic receptors potentiate β-adrenergic activity by producing a sharp increase in intracellular Ca^{2+} and activation of protein kinase C and of prostaglandin (PG) synthesis [61,72,146]. The subcellular mechanisms involved in the initiation and termination of AANAT activity have been elucidated in great detail (see for Ref. [88]). Cyclic AMP stimulates AANAT expression and phosphorylation via protein kinase A, which also allows AANAT to be stabilized by binding of 14-3-3 proteins [47,129]. The nocturnal exposure to bright light suppresses melatonin production immediately by degradation of pineal AANAT [50,70].

Once formed melatonin is not stored within the pineal gland but it diffuses to the blood [141]. In those animals having a deep pineal, like the sheep, melatonin is released into the cerebrospinal fluid (CSF) via the pineal recess to reach high concentrations in the third ventricle, 20–30 times higher than that found in the blood [120].

Melatonin in blood is metabolized mainly in the liver where it is hydroxylated in the C6 position by cytochrome P_{450} monooxygenases (CYPA2 and CYP1A) [26]. It is then conjugated with sulfate to form 6-sulphatoxymelatonin, the main melatonin metabolite found in urine. Melatonin is also deacetylated in neural tissues [57] and is also metabolized to form the kynuramine derivative N^1-acetyl-N^2- formyl-5-methoxykynuramine (AFMK) [44,58,60]. Interestingly this metabolite shares melatonin's antioxidant and anti-inflammatory properties [139]. Melatonin is also converted into cyclic 3-hydroxymelatonin in a process that directly scavenges two hydroxyl radicals [139]. Inasmuch as melatonin freely diffuses through all biological membranes, it exerts its actions in almost all cells in the body. Some of its actions are receptor-mediated while many others are receptor-independent.

Membrane-bound melatonin (MT_1, MT_2) receptors have been identified and cloned from several tissues in the body [37]. These receptors belong to the superfamily of G protein-coupled receptors that contain the typical 7 transmembrane domains [122]. Activation of melatonin receptors in general leads to a decrease in cyclic AMP concentration. A third melatonin binding site, described initially as the "MT_3 receptor", has since been identified as quinone reductase 2 [103].

The distribution of melatonin receptors in lamina I–V and lamina X of the spinal cord was demonstrated by autoradiography [108]. By using reverse polymerase chain reaction techniques, transcripts of both MT_1 and MT_2 melatonin receptors have been identified in both ventral and dorsal horns of the lumbar and thoracic regions of the spinal cord of rats [160]. It was thus hypothesized that melatonin exerts its analgesic effects through activation of melatonin receptors present in both spinal cord as well as in various brain regions.

A combination of reagents derived from the molecular clones and pharmacologic tools have revealed a considerable amount of information about the MT_1 and MT_2 receptors [8]. Many G protein-coupled receptors (GPCRs), including the MT_1 and MT_2 receptors, exist in living cells as dimers. The relative propensity of the MT_1 homodimer and MT_1/MT_2 heterodimer formation are similar whereas that of the MT_2 homodimer is 3–4 fold lower [10,32]. It is of interest that the GPR 50 receptor, though lacking the ability to bind melatonin, abolishes high affinity binding of the MT_1 receptor through heterodimerization [76,77]. Thus the GPR50 receptor may have a role in melatonin function by altering binding to the MT_1 receptor.

Structural modifications of melatonin that seem to predispose to antagonist action include removal of the 5-methoxy group (e.g., luzindole, 2-benzyl-*N*-acetyltryptamine) and the 4-phenyl substituted tetralines, e.g., 4-phenyl-2-propionamidotetraline (4-P-PDOT) [36]. Luzindole was the first ligand to be identified as a competitive melatonin receptor antagonist and has since been used extensively in the field to validate melatonin receptor action. It is relatively receptor type non-selective (MT_1/MT_2 affinity ratio = 16/26) and was the first antagonist to be used for demonstrating that melatonin receptors are involved in the inhibition of dopamine release in rabbit retina and in the phase shift of circadian rhythms in rodents [36]. It must be noted that recent data indicate that luzindole is also an effective antioxidant in vitro [91]