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Review article

Melatonin receptors in humans: biological role and clinical relevance

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Abstract

In addition to its antioxidative effects melatonin acts through specific nuclear and plasma membrane receptors. To date, two G-protein coupled melatonin membrane receptors, MT_1 and MT_2, have been cloned in mammals, while the newly purified MT_3 protein belongs to the family of quinone reductases. Screening studies have shown that various tissues of rodents express MT_1 and/or MT_2 melatonin receptors. In humans, melatonin receptors were also detected in several organs, including brain and retina, cardiovascular system, liver and gallbladder, intestine, kidney, immune cells, adipocytes, prostate and breast epithelial cells, ovary/granulosa cells, myometrium, and skin. This review summarizes the data published so far about MT_1 and MT_2 receptors in human tissues and human cells. Established and putative functions of melatonin after receptor activation as well as the clinical relevance of these findings will be discussed.

Keywords: Melatonin; Melatonin Receptors; Humans; Localization; Biological role; Diseases; Therapy

1. Introduction

Melatonin (*N*-acetyl-5-methoxytryptamine) is primarily synthesized and secreted by the pineal gland [1]. The synthesis of melatonin in the pineal gland involves several steps. Firstly, L-tryptophan, which is taken up from the cerebral vessels, is converted to serotonin. Serotonin is subsequently metabolized by the rate limiting arylalkylamine *N*-acetyltransferase (AA-NAT) to *N*-acetyl-5-hydroxytryptamine. The final step of the synthesis pathway is the conversion of *N*-acetyl-5-HT to melatonin by hydroxyindole-o-methyltransferase. Melatonin is a lipophilic hormone, which is widely distributed throughout the human body [2]. A well-established function of melatonin is its involvement in the regulation of circadian rhythms and seasonal responses. Several research papers from different scientific areas suggest that melatonin may also participate in many other physiological and biochemical functions, which will be presented and discussed in the following chapters of this review.

Four mechanisms of melatonin's action in mammalian species have been described so far [3]. These include:

- binding to intracellular proteins such as calmodulin;
- antioxidative effects;
- binding to nuclear receptors of the orphan family;
- and binding to plasma membrane localized melatonin receptors.

A few reports showed that melatonin can interact with calmodulin, an intracellular protein which is involved in second messenger signal transduction. Melatonin was shown to directly antagonize the binding of Ca^{2+} to calmodulin [4]. Possible antiproliferative effects of melatonin on breast cancer cell proliferation may be partly mediated through this action [5].

The antioxidative, beneficial effects of melatonin have been extensively presented in various pathological conditions associated with free radicals and related reactants, such as ischemia/reperfusion, inflammation, ionizing radiation, mitochondrial toxins, etc. Many comprehensive reviews are available dealing with this topic [6–9].

Melatonin appears to be a natural ligand for the retinoid-related orphan nuclear hormone receptor family (RZR/ROR). RZR/RORα is expressed in a variety of organs, whereas RZRβ is specific for the brain and retina [10]. The third member of

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the RZR/ROR family, called RORγ, is preferentially expressed in human skeletal muscle cDNA [11]. The immunomodulatory effects and possible also part of the circadian effects are partly mediated through this mechanism. For example, it was shown that the activation of these nuclear receptors by melatonin induces the repression of 5-lipooxygenase mRNA expression in human B cell lines [12]. Also the regulation of IL-2 and IL-6 production by human mononuclear immune cells seems to be mediated through this mechanism [13,14]. However, after identification of this nuclear binding site about 10 years ago, research in this area has fallen asleep and was now slightly reactivated in the last years.

In contrast studies about plasma membrane associated melatonin receptors is growing exponentially in the last years (reviewed in [15–20]). Multiple localization sites for the two known melatonin receptors, MT_1 and MT_2, in the human body were published by our group and others in the last decade. Therefore the aim of this review is summarize the data about these localization sites in human tissues. Furthermore, the biological role and clinical relevance of the melatonin receptors will be discussed. The information presented in this review relate to data derived from only human tissue specimens or human cell lines. Findings from rodents or other animals will be specially indicated.

2. Melatonin receptor—pharmacology and signal transduction

Two distinct classes of plasma membrane localized melatonin receptors, which are expressed in humans, have been reported so far, MT_1 and MT_2, formerly designated as Mel_{1a} and Mel_{1b}, respectively [17]. Both types of receptors were identified in a wide variety of tissues with different expression profiles. This will be discussed in detail in the subsequent chapters of this manuscript. All cloned melatonin receptors bind 2-[125I]-melatonin and melatonin at picomolar affinity with K_D values between 25 and 160 pM for ^{125}I-Mel. Due to the availability of cloned MT-receptors there are now an extensive array of agonists and antagonists available [21]. Information about these pharmacological modulators can be obtained in explorative reviews addressing primarily this issue [20,22–24]. In general, no drug exclusively binds one MT-subtype, although some selective drugs have been identified. The best-known agents are luzindol and 4-PDOT, which are presently used to demonstrate MT_2-receptors.

Expression of the cloned MT_1-receptors in various different cell lines (NIH, HEK, CHO) showed that this receptors is coupled to the inhibition of cAMP via Pertussis toxin sensitive inhibitory G_i-proteins. Interactions with several G-proteins (i, o, q, z, 12, 13, 14, 16) were described (reviewed in [16,25]). Activation of the MT_1-receptor leads to inhibition of forskolin stimulated cAMP formation, PKA activity, and phosphorylation of the cAMP-responsive element binding protein, a transcription factor (reviewed in [20]). Relating to animal studies it was, for example, shown that this is an early event in the signaling cascade leading to phase shifts of the endogenous clock [26]. Activation of the MT_1-receptor also i) increases phosphorylation of mitogen-activated protein kinase and MEK1-2 and ERK1/2 probably leading to induction of synthesis of filamentous structures non-neuronal tissues [27], ii) potentiates ATP or Prostaglandin $F_{2\alpha}$-induced phosphoinosite turnover, mediated through the beta, gamma subunits of the heterotrimeric G-protein [28,29], and iii) regulates functional responses of melatonin in ion channels. For example, it was shown that vasoconstriction of rat arteries is mediated by melatonin-induced blockage of calcium activated potassium channels [30]. Also activation of the inward rectifier potassium channel KIR3, which leads to inhibition of neuronal firing in the SCN, is induced by MT_1 activation [31].

Similar to the second messenger pathways of the MT_1 receptor, activation of the MT_2-receptor also inhibits forskolin stimulated cAMP formation [32]. Additionally coupling to this receptor can also lead to inhibition of cGMP formation [33]. Furthermore, in SCN slice, melatonin can increase PKC activity [34].

In addition the both MT-receptors presented, another putative MT_3-receptor was identified on pharmacological grounds with lower melatonin affinity (nM range) in various hamster organs [35]. This MT_3-protein, which shows 95% homology to the human quinone reductase 2, is a detoxification enzyme [36,37]. It has a fast kinetics of association/dissociation and a peak melatonin binding at 4 °C in contrast to the other types of MT-receptors with higher binding rates at rising temperatures [37]. Very little is known about the functions of the MT_3-protein. In a recent study it was suggested that it might be involved in regulation of intraocular pressure in rabbits [38]. Future studies will illuminate further roles and characteristics of this putative melatonin receptor.

Finally a melatonin related receptor (GPR50) was identified recently in mammalians, including humans. This receptor is structurally related to the melatonin receptors, with a 45% homology at the amino acid levels, but is incapable of binding melatonin [39]. In mammals this receptor has been detected in various brain structures and peripheral tissues [40]. The natural ligand for this receptor has not been identified.

The existence of MT_1- and MT_2-deficient mice has been and will be a valuable tool for studying the function of melatonin receptors in various tissues [41,42].

In the next sections localization sites of MT-receptors in various organ systems will be briefly summarized and putative functional roles of melatonin will be discussed.

3. Central nervous system (Table 1)

3.1. Suprachiasmatic nuclei SCN

In humans, expression of the MT_1-receptor subtype in the SCN was first shown by Weaver and Reppert [43]. Transcripts for the MT_2-receptor were not detected in humans but in mice [44]. The role of melatonin in the SCN has been described in several rodent studies and may be also valid for humans. The general opinion is that melatonin is an endogenous synchroni-