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Review Article

The Role of Melatonin and Melatonin Receptors in Pharmacology and Pharmacotherapy of Cancer

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Abstract

Melatonin is a neurochemical hormone produced by pineal gland and has an important role in regulating circadian rhythm in human body. In recent years it has revealed some cytoprotection and antimitogenic effect of this neurohormone which was explained in relation to its receptors and accordingly some intracellular signaling pathways. The Role of melatonin in some important cancers as breast and colon cancer has been administrated clearly, and some other studies are being conducted for some other important malignancies. This paper describes some anticancer aspects of melatonin and its receptors.

Keywords: Melatonin; Melatonin receptors; Breast cancer; Colon cancer; Signalling pathways

Introduction

Melatonin (N-acetyl-5-methoxytrypamine) was discovered 50 years ago by Lerner et al. who extracted this indolamine from the bovine pineal gland and found that it caused the lightening of the frog skin known as depigmenting factor by McCord and Allen in 1917. Then chemical structure of this compound as N-acetyl-5-methoxytrypamine was determined and shown to act as an antagonist of the a-melanocyte stimulating hormone (a-MSH) [1].

The synthesis of melatonin is in multistep pathways, which begins with hydroxylation of aromatic amino acid L-tryptophan to 5-hydroxytryptophan catalyzed by tryptophan hydroxylase. 5-hydroxytryptophan is then converted to serotonin (5-hydroxytryptamine) by the aromatic amino acid decarboxylase. Serotonin is subsequently converted to N-acetylserotonin by the enzyme arylalkylamine N-acetyltransferase. The final step of synthesis is the conversion of N-acetylserotonin to melatonin by hydroxyindole-O-methyl transferase [2]. The biosynthetic pathway of melatonin is shown in Figure 1.

In mammalians, the role of melatonin consists of controlling circadian rhythm and acting as a neuromodulator, hormone, cytokine and biological response modifier [1]. It has also some effects on CNS, immune, gastrointestinal, cardiovascular, renal, bone and endocrine functions, and has some properties as an oncostatic and anti-aging compound [1].

Melatonin's actions are through its interaction with specific membrane bound receptors. As anticonvulsant and vasoconstrictor activity with the activation of MT1 receptors, and vasodilatation with the activation of MT2 receptors [3]. It has also been revealed that melatonin has a protective effect against myocardial infarction, and also can inhibit weight gain and reduce the effects of estrogen [4].

Moreover, Melatonin can induce some non-receptor mediated mechanisms, as scavenger for reactive oxygen and nitrogen [1-5]. The reactive species scavenges include hydroxyl radical, hydrogen peroxide, nitric oxide and many others [1]. Melatonin acts not only as a potent antioxidant, but also as a potent cytoprotective agent [6]. At normal concentrations, melatonin antagonizes oxidative stress and controls cellular metabolism [7].

Melatonin, after being produced in the pineal gland and entering blood circulation, plays as an endocrine hormone and a chemical transmitter of light and darkness [8]. Some findings have shown that in bone marrow, lymphocytes, and the skin, it can produce some signals which protect these organs from free radical-mediated damage [9].

Since melatonin discovery, some roles of melatonin, such as the regulation of circadian rhythms, acting as a neurotransmitter or a hormone to regulate numerous organ systems, and as an antioxidant, have been recognized [10]. Many of these roles act through G protein coupled membrane receptors: (MT1 and MT2) and some of them are independent from receptor [11].

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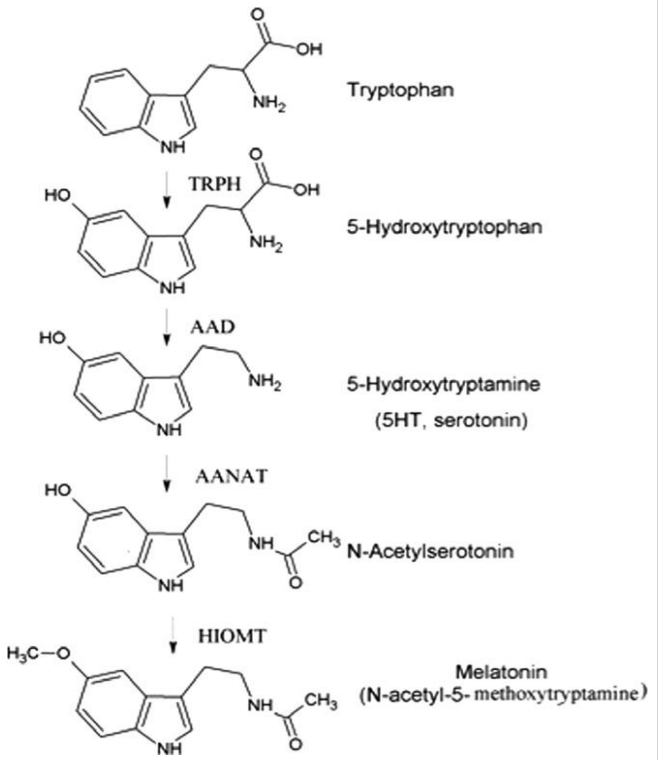

Figure 1: The biosynthetic pathway of melatonin. Melatonin is synthesized from tryptophan in a multistep process [1].

Melatonin also affects the retinoic acid family of nuclear receptors and produces many effects [1]. More studies are needed to find out how it controls these receptors. According to crystal structure of ROR receptors, cholesterol sulphate, but not melatonin, was found as its natural ligand [10]. Other compounds were also found as potent ligands for RORa nuclear receptor including cholesterol derivatives; however, melatonin was not among them [11,12]. Some scientists guess melatonin indirectly controls nuclear receptors through MT1 membrane receptor when activated by melatonin [13].

With the knowledge improvement, molecular and genetic tools are being used to find melatonin receptor expressions and their physiological roles in physiology and diseases. These receptors can be pharmacological goals for immunomodulation, regulation of endocrine functions, anti-cancer activity, circadian activity, cardiovascular physiology, skin pigmentation, hair growth and aging. Thus, developing the knowledge of expression, regulation, signaling and function of melatonin receptors in peripheral cells and tissues may contribute to pharmacotherapy of different kinds of diseases [1].

In vitro studies showed that MLT can have a direct and an indirect anti-oxidative effect [14]. In the direct way, it inactivates hydroxy (.OH) and superoxide ($.O_2$), confirming that it is a potent free radical scavenger [14]. Indirectly, melatonin (MLT) has been found to alleviate nephro-, cardio- and myelotoxicity of doxorubicin (DOX) and other anthracyclines in vivo; yet few data are available to show the effects of MLT on the cytotoxicity of antineoplastic drugs toward tumor cells *in vitro*.

According to numerous reports, MLT may protect cells of various organs against the damage from ROS-producing chemicals due to its potent anti-oxidative effects [15].

The Role of Melatonin in Cancer

It has been discovered that melatonin has oncostatic efficacy on hormone-related mammary cancer [16,17]. Some manipulations which activated pineal gland, or taking melatonin from animals, diminished the growth rate of chemically mammary tumors in rodents, while pinealectomy or decrease of melatonin production stimulated mammary cancer [16,17]. Melatonin decreases the incidence of breast cancer by down-regulating the synthesis of some hormones necessary for normal or pathological growth of the mammary gland [16,18] and through direct actions on the tumor cells [16,18-20].

Some researches' findings on animal models and human breast cancer cell lines confirm the idea that melatonin anticancer effects on hormone-dependent mammary tumors are mainly dependent on its efficacy to act through estrogen-signalling pathway of tumor cells [18,21]. At the mammary tumor cell level, melatonin interacts with the estrogen-response pathway and counteracts the effects of estrogens so it can act as a selective estrogen receptor regulator. Melatonin has this modulator efficacy due to its anti aromatase activity [16].

Generally, the effects of melatonin on cancer cells have been demonstrated by a mechanism not only dependent on its binding to receptors (in membrane or nuclei of cells) but also independent from receptors (binding to calmodulin or by its antioxidant effects) [22,23].

In mammary cancer cells, aromatase genes consisting of promoters controlled by cAMP [12,24-26] and some agents as melatonin has the ability to decrease cAMP levels, and can decrease aromatase activity. Also, the overexpression of the melatonin receptor (MT1 receptor) potentiates the growth-inhibitory effects of melatonin in ER•-positive (MCF-7) human breast cancer cells [16].

Breast Cancer

It has been shown that melatonin administration can decrease and in some cases increase or have no effect on the progress of the mammary gland tumors in mice and rats [1]. Also in the breast tissue, melatonin receptors can control estrogen receptor binding [1]. In recent years, it has been demonstrated that MT1 receptor is expressed in MCF-7 and MDA-MB-231 (human breast cancer cell lines) and in the breast cancer tissues [1,27-29]. In MCF-7 cells, melatonin reversibly prevents cell proliferation and cell invasion [30]. There is a crosslink between MT1 receptor and estrogen receptors' pathways in the breast cancer tissues [31]. The MT1 expression is downregulated by exogenous estradiol and melatonin in MCF-7 cells. Moreover, the MT1 receptors' expression is upregulated in the estrogens' receptors' negative cells (MDA-MB-231) and downregulated in the estrogens' receptors' positive cells (MCF-7) [32].

The role of melatonin in breast cancer etiology has been found in 1970s; other studies have provided some evidence that melatonin could inhibit breast tumor progress [33]. Melatonin plays its role in etiology and progression of cancer through a number of mechanisms, including direct anti-proliferative effects on breast cancer cells, interaction with the estrogen pathway, activating immune system and interactions with estrogen and insulin pathway members [33]. The melatonin receptors 1a and 1b (MTNR1a and MTNR1b) are,

respectively, largely responsible for mediating the downstream effects of melatonin, while Aryl-Alkyl amine-Nacetyltransferase (AANAT), which is the important enzyme in melatonin synthesis and regulates the day/night rhythm of producing melatonin in the pineal gland, can have a similar role [33]. It was demonstrated that these three genes or proteins are potentially important agents in making the risk of breast cancer [33].

According to some studies, physiological concentrations of melatonin inhibit *in vitro* growth of estrogen receptor, a (ERa)-positive breast cancer cells as MCF-7 cells [34] In vivo studies, revealed that experimental manipulations activating the pineal gland or exogenous administration of melatonin reduced the incidence and the growth of carcinogen-induced mammary tumors in rats and mice [34-36] but pinealectomy or other ways which reduced systemic melatonin levels in animals increased mammary tumor incidence [34, 37]. Generally, melatonin produced by mechanisms dependent upon receptor activation or receptor-independent as antioxidant effects and calmodulin-mediated can prevent the progress of cancer in mammary tumors [34]. Besides, some of melatonin receptor-related mechanisms may have the same result as its metabolites [34]. The activation of the MT1 melatonin receptor by melatonin can affect a variety of G proteins which activate some down-stream signal transduction pathways.

Yuan L. and his colleagues have reported [34,38,39] that the majority of the growth-inhibitory actions of melatonin on breast cancer cells appear to be mediated through the MT1 G protein-coupled membrane melatonin receptor. They reported that in MCF-7 breast cancer cells, melatonin inhibits estrogen, forskolin or Pituitary Adenylate Cyclase-Activating Polypeptide (PACAP) which increases cAMP levels through activation of the membrane G protein-coupled MT1 receptor [39]. So it was found that melatonin can regulate the transcriptional activity of a number of steroid receptors, including ERa, which can play an important role in progression of breast cancer [40]. The antiproliferative effect of melatonin appears to be partially mediated through mechanisms involving modulation of the ERa signaling pathway, such as down-regulation of ERa expression [41] and increase in estrogen-induced ERa transcriptional activity which affect the expression of growth-modulatory, estrogen-regulated genes [34].

In contrast, many pineal indolamines that are precursors (serotonin, N-acetylserotonin) or enzymatic degradation products of melatonin have not been found to inhibit the proliferation of breast cancer cells [34].

Abd El-Aziz et al. [42] has shown that the co-treatment of melatonin and 9-cis Retinoic Acid (9cRA) can inhibit the development, delay the onset and induce the regression of mammary tumors; based on the fact that the combination of S23478-1 (a new non-selective MT1 and MT2 agonist) and antRA (retinoic acid antagonist) can induce apoptosis in human breast tumor cell lines [42].

Recently, Cucina et al. has shown that with administration of melatonin and MT agonist, the highest expression of Bcl-2 and Bax and the lowest level of MT1 receptor expression can be observed. According to their study, the pro-apoptotic effect of melatonin in MCF-7 cells can explain the biphasic apoptotic event triggered by melatonin: an early (24hr) TGFb1 and caspase-independent apoptotic response associated with an increased Bcl-2/Bax ratio, and a late (96 hr) TGFb1 and caspase-dependent process with a concomitant decrease in Bcl-2/Bax ratio [43]. He observed decreased Bcl-2 and increased Bax levels in the mammary tumors treated with melatonin or melatonin agonist S23478-1 which may have the same result as the late apoptotic process activated by melatonin [34,43].

Melatonin receptors in the gastrointestinal tract

The first finding about melatonin activity in the GI tract by Quastel and Rahamimoff demonstrated that melatonin diminished the spontaneous contraction of the intestine [1,44]. Now it is clear that melatonin, not only exists in the GI tract but also, based on some findings, it is produced locally by intestine with two enzymes, AANAT and HIOMT, which are expressed in the intestine epithelial. Moreover, it has been shown that its concentrations can be 10 to 100 times more in the intestine than in the serum [1,44].

Melatonin may have many important effects on the gut. It can act as a physiological antagonist of serotonin [1]. Although this mechanism has not been completely cleared, there exist two theories: the blockade of serotonin through the CCK2, 5HT3 and MT2 receptors, through which melatonin can inhibit serotonin's action [1]. Also, it has been found that melatonin's secretion is increased in the intestine during fasting [1]. Melatonin can also activate the secretion of mucosal bicarbonate by inducing calcium release in the enterochromaffin cells [45]; this effect seems to be mediated by the MT2 receptor [1,45]. Melatonin has also been shown to activate the pancreatic secretion of amylase and cholecystokinin via activating MT2 receptors [45,46]. Moreover, melatonin can have considerable receptor-independent activities in the GI tract as a free radical scavenger [47]. Recently, the preventive role of melatonin against ulcer formation and its curing has become well known [1,48].

Melatonin receptors in the gut

Melatonin receptors are distributed along gastrointestinal tract and have some physiological effects by activating some specific membrane receptors (Mel1A, Mel1B and Mel1C) [49]. Mel1A and Mel1B were recently renamed as melato¬nin-1 receptor (MT1) and MT2 receptor [49].

Besides, there are a number of nuclear melatonin receptors belonging to the Retinoid Z Receptor (RZR) or Retinoid Orphan Receptor (ROR) subfamilies with three subtypes (α, β, γ) [49]. There is an interaction between membrane and nuclear melatonin receptors; this finding has confirmed that the expression of ROR/RZR mRNA is decreased in blood mononuclear cells with a reduced MT1 receptor expression. Also, melatonin can directly interact with intracellular proteins such as calmodulin, calreticulin or tubulin [49].

According to one research using tissues from rat pancreas, stomach, duodenum and colon, it was recognized that there were some high levels of MT2 receptors in the colon which shown by western blot analysis [50]. In the same study, the most MT2 immunoreactivity became known in the muscularis mucosae and in circular and longitudinal muscle layers of animal gut [49]. With investigation of MT2 receptors in the intestinal muscle layers, Involvement [50]. Compared to MT1, the expression of MT2 receptors has not been affected by food intake.

Some pharmacological animal studies also indicated the presence of the melatonin MT3 receptors in colon [51,52].

In addition, in blood vessels of both rodent and human colon, a high density of melatonin-binding sites was reported. *In vitro* preparations of arterial smooth muscle of the porcine colon relaxes in response to melatonin and melatonin receptor agonists; however these effects were observed at rather high concentrations of melatonin [53].

Although there are some data showing the localization and expression of MT receptors in GI tract, the presence of nuclear melatonin binding sites has not been completely observed yet. Some studies suggest that these nuclear receptors are present in murine colon cancer cells, but the details of this thesis and the precise localization of these receptors remain unclear [49,54].

Colon Cancer

With identification of melatonin binding sites among the patients with carcinoma in human colon and rectum, the possible role of melatonin in colorectal cancer was identified through several studies [49]. Melatonin binding sites were identified in the mucosa and submucosa of the human colon and radioimmunoassays have shown that melatonin's concentrations of tissue in non-cancer control patients are lower than melatonin concentrations in the colon of patients with colorectal carcinoma [55]. Colorectal carcinoma patients shown significant decline in the peak level of melatonin secretion, as well as a reduction in overall melatonin output [56]. Some researchers have demonstrated that melatonin can be involved in colon cancer risk or preventing the progress of this kind of cancer [49,57].

It was surprisingly found that pinealectomy can enhance the colonic crypt cell proliferation in rats, suggesting that melatonin pathways can be involved in carcinogenesis in colon [49].

Controlling mechanism of melatonin in colon involves inhibition of tumour angiogenesis, the modulation of the mitotic and apoptotic activity, and regulating cellular concentrations of glutathione [49,58-60]. Another suggestion for melatonin effects is according to the regulation of estrogen receptors. Also direct effects on the cell cycle, influencing several growth factors and enhancing gap junctions and increasing intracellular concentrations of anti-oxidants can be considered for its protective mechanism [49,61,62]. Some researches indicate that, in colon adenocarcinoma, membrane-bound and nuclear melatonin receptors are involved in their oncostatic properties [16, 63]. Also melatonin can regulate immune reactivity by binding to receptors on T helper cells and monocytes and therefore stimulate the production of INFγ and interleukins 1, 2, 6 and 12 [64]. Melatonin in this way can also regulate the expression of NF-κB, TNF-α, IL-1β and STAT3 [65,66]. Melatonin, also in other routes, can activate lymphocytes and monocytes/macrophage system in which it can act as an immunosurveillant to prevent tumor progression [49,67,68].

In clinical trials, melatonin was shown to have cytoprotective effects that may be involved in increasing the efficacy of cancer chemotherapy and improving survival [49]. Also, according to many studies, adding melatonin to chemotherapy treatment can reduce the toxicities of chemotherapy and radiotherapy in patients with colorectal carcinoma [49].

Also, based on our recent researches, we have found that serotonergic receptors (5H1A,1B,3,4) are expressed clearly in colorectal cancer cells [69-71]; moreover, we have had some new researches to study melatoninergic receptors (MT1 ,MT2 and ROR) expression in adenoma carcinoma tissues. In our recent study, we have shown that MT2 receptor has been expressed in gastric adenocarcinoma human tissues significantly [72,73]. Also in another study we have shown that melatonin could have inhibitory effect on cell proliferation of AGS and MKN49 gastric adenocarcinoma cell lines [74]. Some results from our other studies, especially related to MT1 receptor expression are under reviewing or publishing.

Conclusion

According to several studies, melatonin can have anti-cancer effect, especially in breast and colon cancer and recently there are some evidences about its' role in gastric cancer. Melatonin can induce this effect through its membrane or nuclear receptor and the subsequent intracellular signalling pathways. Melatonin plays its role in the etiology and progression of breast cancer by a number of mechanisms, including direct anti-proliferative effects on breast cancer cells, interaction with the estrogen pathway and activating immune system. In GI tract, melatonin concentration in the ileum and the colon depends on food intake and digestion. Melatonin is also involved in immunomodulatory functions in the gut. It can also inhibit or regulate serotonin receptors in GI tract.

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