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Melatonin: functions and ligands

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Melatonin is a chronobiotic substance that acts as synchronizer by stabilizing bodily rhythms. Its synthesis occurs in various locations throughout the body, including the pineal gland, skin, lymphocytes and gastrointestinal tract (GIT). Its synthesis and secretion is controlled by light and dark conditions, whereby light decreases and darkness increases its production. Thus, melatonin is also known as the 'hormone of darkness'. Melatonin and analogs that bind to the melatonin receptors are important because of their role in the management of depression, insomnia, epilepsy, Alzheimer's disease (AD), diabetes, obesity, alopecia, migraine, cancer, and immune and cardiac disorders. In this review, we discuss the mechanism of action of melatonin in these disorders, which could aid in the design of novel melatonin receptor ligands.

Introduction

Circulating melatonin (5-methoxy-*N*-acetyltryptamine) in mammals is largely derived from the pineal gland [1,2], although other organs producing melatonin include the GIT, epithelial hair follicles, skin, retina, salivary glands, platelets, lymphocytes and developing brain [3,4]. It performs a clock and calendar function in body. Along with antioxidant actions, melatonin is a biological modulator of mood, sleep, sexual behavior and circadian rhythm. Low levels of melatonin have been shown in Parkinson's disease (PD), AD, insomnia, epilepsy, ischemic injury and neuropsychiatric disorders; in addition, roles for melatonin in the development of cataracts, aging and retinitis have also been reported [5,6].

Melatonin is a derivative of tryptophan and was discovered by Aron B. Lerner in 1958 [7]. It is synthesized mainly in the pineal gland by parenchymatous cells in response to light information received through retinohypothalamic pathways. Further light information reaches the suprachiasmatic nucleus (SCN) where the circadian clock exists. This enables the synchronization of the phases of the circadian clock with the light–dark cycle. Information relating to time passes from the SCN to the superior cervical ganglion and finally to the pineal gland. This pathway is stimulated during the night and the activity of the superior cervical region is inhibited by light stimulation. Noradrenaline is secreted by nerve terminals from the superior cervical region and activates β receptors on the pineal gland. As a result, synthesis of cAMP increases, which enhances the activity of either aralkylamine *N*-acetyltransferase (AANAT) or serotonin *N*-acetyltransferase (SNAT), rate-limiting enzymes in melatonin synthesis. These enzymes convert serotonin into *N*-acetyl serotonin, which with the additional help of hydroxyindole-*O*-methyl transferase (HIOMT), also known as acetyl serotonin *N*-methyltransferase (ASMT), is converted to melatonin (Fig. 1) [8,9].

Melatonin is metabolized mainly in liver via hydroxylation at the sixth position by cytochrome P450, family 1, subfamily A, polypeptide 1 (CYP1A1) and cytochrome P450, family 1, subfamily B, polypeptide 1 (CYP1B1). After hydroxylation, melatonin is excreted as a sulfate conjugate, although glucuronide conjugation can occur. Melatonin is deacetylated in the pineal gland and retina by melatonin deacetylase. In other cells, it can be metabolized by free radicals and is converted to cyclic 3- and 6-hydroxymelatonin [10]. N^1-Acetyl-N^2-formyl-5-methoxykinuramine (AFMK) and N^1-acetyl-5-methoxykinuramine (AMK) are two important melatonin metabolites that have excellent radical scavenging activity. AMK is predicted to be better than melatonin in scavenging hydroxyl radicals and their scavenging efficiency depends on the radical with which they are reacting (Fig. 2) [11,12].

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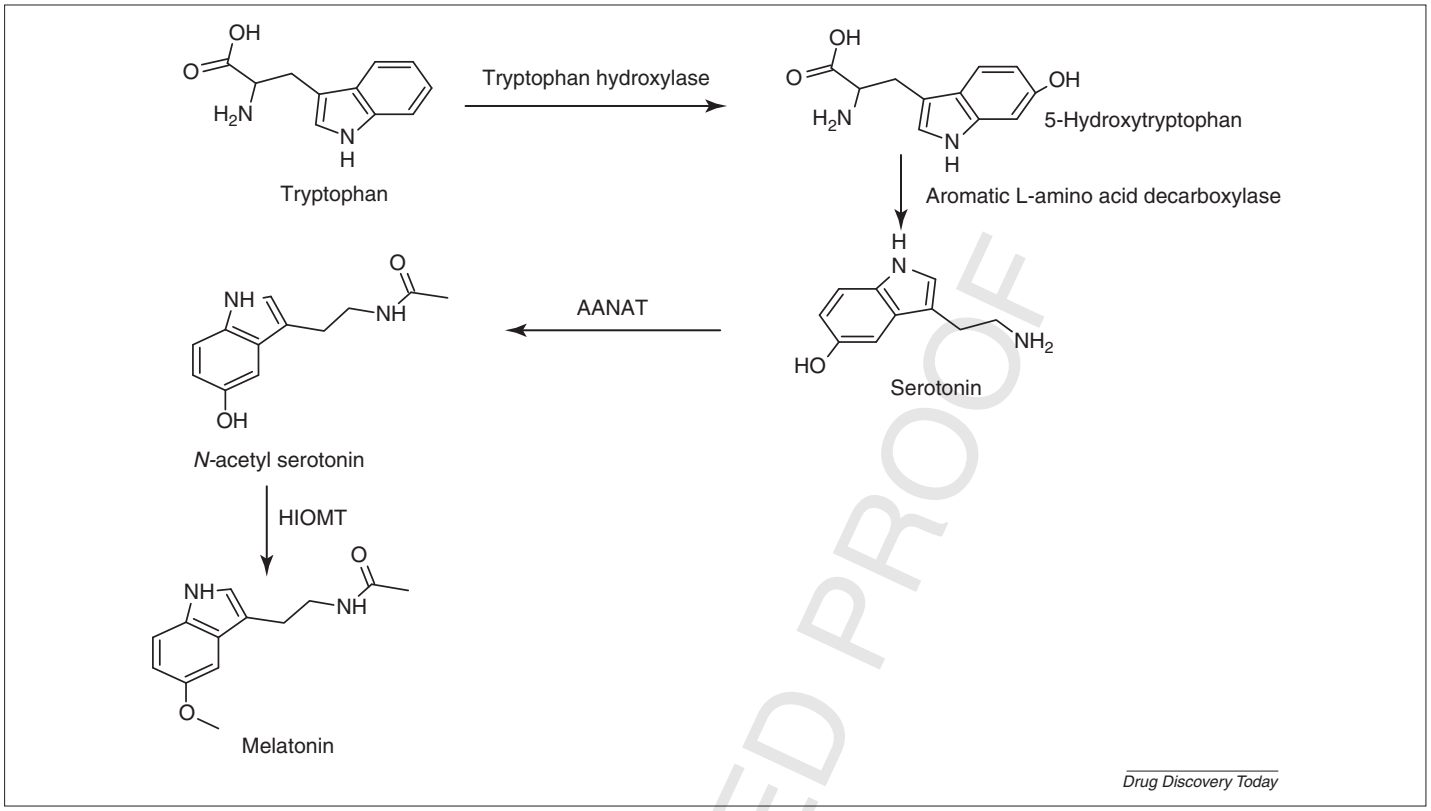

FIGURE 1

Melatonin biosynthesis from tryptophan. Tryptophan is converted via hydroxylation to 5-hydroxy tryptophan, which is further converted to serotonin utilizing an aromatic L-amino acid decarboxylase enzyme. Serotonin is further acetylated by the enzymes aralkylamine *N*-acetyl transferase (AANAT) or serotonin *N*-acetyltransferase (SNAT). Finally, with the help of either hydroxy indole-*O*-methyl transferase (HIOMT) or acetyl serotonin *N*-methyltransferase (ASMT), the biosynthesis of melatonin occurs.

Melatonin receptors and signaling

Melatonin receptors are G protein-coupled seven transmembrane receptors and have two subtypes (MT1 and MT2) expressed in SCN, hippocampus, substantia nigra and ventral tegmental area. Intracellular signaling is mediated through modification of activities of adenylate cyclate, phospholipase C (PLC), guanylate cyclase, and calcium and potassium channels [13]. Melatonin also binds to the MT3 receptor (quinone reductase II), which is thought to be a molecular target for antimalarial drugs, such as chloroquine. Indirectly, melatonin might function through orphan receptors from the retinoid orphan receptor (ROR)-α and retinoid Z receptor (RZR) family [14]. MT1 receptors are expressed in retina, ovary, testis, mammary gland, coronary arteries, gall bladder, aorta, liver, kidney, skin and the cardiovascular system (CVS) [15,16]. MT1 receptors were cloned almost 20 years ago from sheep and humans and are 350 amino acids long. MT1 receptor activation inhibits adenyl cyclase, which decreases cAMP production and reduces protein kinase activity. The outcome of these events is phosphorylation of cAMP responsive element-binding protein (CREB). The MT1 receptor also activates phospholipase, which regulates ion flux inside the cell.

The MT2 receptor was cloned in 1995 from brain retina and human pituitary gland and is 363 amino acids long, with two exons and one intron in the gene. Binding of melatonin to the MT2 receptor inhibits adenylyl cyclase and decreases cAMP [17,18]. Through the MT2 receptor, melatonin also inhibits guanylyl cyclase and reduces the formation of cGMP; in addition, through PLC, melatonin affects the protein kinase that is responsible for ion flux inside the cell. MT3 receptors have not yet been identified in humans, although they are expressed in hamster, mainly in liver and kidney but to a lesser extent in heart, adipose tissue and brain [18,19].

Melatonin as an antioxidant

In organisms with aerobic metabolism, molecular oxygen is converted to water, which is an essential and unavoidable process. From mitochondria, which are the major source of energy reactions, electrons are released to the respiratory system, where they are involved in the formation of hydrogen peroxide radicals (H_2O_2), superoxide radicals (·OOH) and hydroxyl radicals (·OH). These free radicals are known as reactive oxygen species (ROS) and can damage the DNA. This affects the physiology of aging and oxidation of polyunsaturated fatty acids, lipids, amino acids and various cofactors [18]. Radical formation is the key reaction in many diseases involving neurodegeneration, and immune, inflammatory and mitochondrial diseases [20]. The electrophiles and radicals generated and their metabolic products not only cause damage to cellular components, but can also result in mutations leading to alterations in structural proteins and signaling pathways [21]. Melatonin also stimulates the synthesis of glutathione, which is another antioxidant that reduces electron leakage from the mitochondrial electron chain [22]. Melatonin is

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