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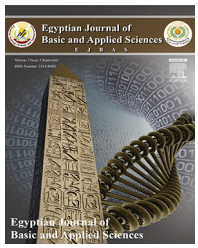

Review Article

Advancing role of melatonin in the treatment of neuropsychiatric disorders

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ABSTRACT

Melatonin is a pineal neurohormone whose secretion is influenced by circadian changes of 24 hour night and day cycle. Over the recent past, several studies have highlighted the ubiquitous influence of the circadian timing in almost all the physiologic functions. An altered/deficient sleep–wake cycle has been correlated with physiological imbalances which are linked to the development of various disorders, viz depression, anxiety, psychosis, attention deficits, sleep deprivation and others. Melatonin and its oxidation products, viz cyclic 3-hydroxymelatonin, N1-acetyl-N2-formyl-5-methoxykinuramine and N1-acetyl-5-methoxykinuramine possess excellent antioxidant properties. Melatonin's beneficial neuroprotective properties are mostly attributed to excellent free radical scavenging properties. A gathering body of evidence has shown that besides strong antioxidant activities, melatonin is a pleiotropic regulator molecule which orchestrates multiple functions through all the three melatonin receptors, i.e. MT_1, MT_2, and MT_3. For example, MT_2 receptor agonistic activity is attributed to neuroprotective, hypnotic and anxiolytic properties while MT_1 and MT_2 agonistic activity is associated with the clinical efficacy of agomelatine. The third melatonin receptor has been identified as quinone reductase (QR) 2, an enzyme involved in detoxification. MT_3 agonist has been linked to strong hypotensive effects in preclinical study.

In conclusion, the gathering body of evidence both from preclinical and clinical literatures suggests strong antioxidant activities and diverse pleiotropic mechanisms of melatonin for potential neuroprotective role in diverse neuropsychiatric disorders. However, there is still a lack of melatonergic ligands with high selectivity and specificity to precisely target any particular neuropsychiatric disorders for which limited therapeutic options are currently available clinically.

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1. Introduction

Melatonin (*N*-acetyl-5-methoxytryptamine) is regarded as a human time-keeping machine and is also referred to as the hormone of darkness. It performs clock and calendar functions to make the human body adapt to diurnal variation which influences the 24-h rhythms in human physiology and behaviors. In 1958, Lerner and colleagues isolated and chemically characterized melatonin in the mammalian pinealocytes [1]. Lately, because of the involvement of melatonin in many physiological and behavioral functions such as sleep–wake cycle, hormonal secretion, thermoregulation, and other physiologic events, melatonin is now called pleiotropic neurohormone [2]. Melatonin has also been reported to regulate feeding behavior, energy metabolism, free radical scavenging, immunity, maintenance of vasculature, inflammation, cancer cell proliferation, reproduction, growth and development, and aging [3].

1.1. *Physiological response of melatonin and suprachiasmatic nucleus*

Suprachiasmatic nucleus or nuclei (SCN), a tiny region located in the anterior part of the hypothalamus and situated directly above the optic chiasm, is called as master circadian-pacemaker or the central body clock of mammals responsible for controlling circadian rhythms. The activity of SCN is governed by the expression of clock genes. Signals from SCN travel along multiple-synaptic pathways, involving complex intrahypothalamic connection, to control circadian rhythm via the regulation of melatonin secretion [4]. Light activates photosensitive, melanopsin-containing, retinal ganglion cells, which are sensitive to short-wavelength visible light and communicate the information directly to SCN via the retinohypothalamic tract (RHT). Neuronal axons in RHT release the glutamate and pituitary adenylate cyclase activating polypeptide (PCACP), mediating clock gene expression in SCN. Inhibitory projections (γ-aminobutyric neurons) in SCN send a direct inhibitory projection to paraventricular nucleus (PVN) of the hypothalamus. Neuronal cells in PVN activate preganglionic neurons of intermediolateral cell column which control the sympathetic output to the pineal gland regulating the secretion of melatonin by the pineal gland [5–7]. Melatonin is primarily produced by the pineal gland from amino acid tryptophan. Small amounts of melatonin is also produced in gut, Harderian gland, bone marrow, epithelial hair follicles, skin, retina, salivary glands, platelets, lymphocytes and developing brain but the physiological significance of melatonin from these extrapineal sites, except retina, is still a matter of debate. Norepinephrine (NE) is the major neurotransmitter involved in the regulation of arylalkylamine *N*-acetyltransferase (AANAT), the rate limiting enzyme in melatonin synthesis. There are two pathways involved in the synthesis and release of melatonin which are stimulated by NE. The first is β_1-adrenergic/cyclic adenosine monophosphate (cAMP)/protein kinase A (PK_A) activation, and the second involves α_1-adrenergic/calcium [Ca^{2+}] pathways. Activation of β_1 receptors increases cAMP concentration, intracellularly, leading to the activation of cAMP-dependent PK_A. Both elevated cAMP levels and PK_A activation are critical for stimulation of AANAT. Secondly, the activation of α_1 receptors leads to increases in the intracellular calcium concentration ($[Ca^{2+}]_i$) by the release of calcium ions from intracellular stores followed by Ca^{2+} influx into the pinealocytes [8]. Amino acid tryptophan, the precursor for melatonin synthesis, is actively up taken into the pinealocytes, hydroxylated and decarboxylated to serotonin. During the day, serotonin in pinealocytes is stored, and remains unavailable to enzymes (monoamine oxidase and melatonin-forming enzymes) which would otherwise act on it. With the onset of darkness, postganglionic sympathetic outflow to the pineal increases which causes the release of NE and the subsequent activation of adrenergic receptors on pinealocytes causes stored serotonin to become accessible for intracellular metabolism. Melatonin is produced by the metabolism of serotonin into in two steps which are catalyzed by AANAT or serotonin *N*-acetyltransferase (SNAT) and hydroxyindole-O-methyltransferase (HIOMT) or acetylserotonin *N*-methyltransferase (ASMT). *N*-acetylation of serotonin by AANAT produces *N*-acetylserotonin (NAS) and O-methylation of NAS by HIOMT, eventually, produces melatonin (Fig. 1) [8,9].

1.1.1. *Melatonin receptors*

Melatonin mediates physiological effects via MT_1 and MT_2 melatonin receptors which are specific G-protein coupled receptors. MT_1 receptor is reported as sensitive to the pertussis toxin while MT_2 melatonin receptor is reported as sensitive to the cholera toxin. MT_1 and MT_2 receptors are expressed in the central nervous system (CNS), including, hippocampus, ventral tegmental areas, and SCN. Additionally, MT_1 receptor also expresses in retina, ovary, testis, mammary gland, coronary arteries, gall bladder, aorta, liver, kidney, skin and the cardiovascular system and MT_2 melatonin receptor in retina and human pituitary gland [8,10]. Melatonin mediated intracellular signaling involves modification of the activities of adenylyl cyclase (AC), phospholipase C (PLC), guanylylcyclase (GC), cyclic guanosine monophosphate (cGMP) as well as calcium and potassium channels [8,10,11]. Physiological responses associated with MT_1 receptor activation include the modulation of neuronal firing, arterial vasoconstriction, cell-proliferation in cancer cells, reproductive and metabolic functions [10], and MT_2 receptor associated physiological responses include the phase shift circadian rhythms of neuronal firing in the SCN, inhibition of dopamine release in retina and leukocyte rolling in arterial beds, induction of vasodilatation, and enhancement of immune responses [11]. Two additional proteins were also reported as melatonin receptors or melatonin receptor modulators. A third melatonin receptor, MT_3, was also identified which binds to quinone reductase 2 (QR2). GPR50 is another melatonin-related protein having 45% similarity to human MT_1 and MT_2 receptors. GPR50 does not directly bind to melatonin but it influences the binding of melatonin to MT_1 receptor [12]. A deletion of GPR50 has been genetically linked to psychiatric disorders such as bipolar disorder and major depression [13].

1.1.2. *Melatonin metabolism*

Metabolism of melatonin (Fig. 2) primarily takes place in hepatic cells with the aid of cytochrome P450, family 1, subfamily A, polypeptide 1 (CYP1A1) and cytochrome P450, family 1, subfamily B, polypeptide 1 (CYP1B1). However, it was reported that CYP1A2 and, to some extent, CYP2C19, are primarily respon-