HOSTED BY

ELSEVIER

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: http://ees.elsevier.com/ejbas/default.asp

Review Article

An insight into the scientific background and future perspectives for the potential uses of melatonin

Md Jamir Anwar[*], *Bala Yauri Muhammad*, *Ahmed Abdulsabour Bader*, *Mahfoudh Abdulghani*, *Danish Mahmood*, *Mohammed Haider*

Department of Pharmacology and Toxicology, Unaizah College of Pharmacy, Qassim University, Al-Qassim, Kingdom of Saudi Arabia

ARTICLE INFO

Article history:
Received 17 March 2015
Received in revised form
6 May 2015
Accepted 8 May 2015
Available online 27 May 2015

Keywords:
Antidepressant
Antiepileptic
Antiosteoporotic
Antioxidant
Cardiovascular disease
Circardian rhythm
Hypnotic
Immunodulatory
Melatonin

ABSTRACT

Melatonin is one of the most versatile and ubiquitous molecule widely distributed in nature has been reported to play a role in a wide variety of physiological responses including reproduction, circadian homeostasis, sleep, retinal neuromodulation, and vasomotor responses. In most vertebrates, including humans, melatonin is synthesized primarily in the pineal gland and is regulated by the environmental light/dark cycle via the suprachiasmatic nucleus. Melatonin is synthesized in all areas of the body such as gastrointestinal tract, skin, bone marrow, retina and in lymphocytes, from which it may influence other physiological functions through paracrine signalling. In addition to regulation of circadian rhythm of melatonin a variety of other physiological effects such as hypnotic, antidepressant, antiepileptic, oncostatic, immunomodulatory, antiosteoporotic, in cardiovascular disease, neuromodulatory and cerebral ischaemic condition have been reported. Moreover there is scarcity of literature that reviewed the scientific evidence for its use in these conditions. Therefore in this article we review recent advances in this research field, which is preceded by a concise account of general information about melatonin, melatonin receptors and intracellular signalling pathways for melatonin actions.

1. Introduction

Melatonin (N-acetyl-5-methoxytryptamine) was isolated from the bovine pineal gland 55 years ago [1,2]. The rhythmic production of melatonin by the pineal gland was initially linked to the regulation of seasonal reproduction in photoperiodic species [3,4]. Subsequent studies have shown that melatonin's functions greatly exceed that of regulation of the waxing and waning of seasonal reproductive competence [5,6].

Seasonal reproduction is an adaptive physiological process utilized by animals that live under natural environmental conditions to anticipate annual changes in day length, temperature and food availability [7]. This allows them to make the necessary physiological adjustments in advance of the actual sexually quiescent interval or breeding period [8]. In

* *Corresponding author*. Tel.: +966 501071895.
E-mail addresses: m.anwar@qu.edu.sa, zameeranwar@gmail.com (M.J. Anwar).
Peer review under responsibility of Mansoura University.
http://dx.doi.org/10.1016/j.ejbas.2015.05.003

mammals, photoperiodic information is received at the level of the ganglion cells of the retina and is transmitted via a multi synaptic neural pathway to the pineal gland where the message modulates the rhythm of melatonin secretion [9]. A major function of the melatonin rhythm is to transmit information about length of the daily dark period to the circadian and circannual systems; thus it provides time-of-day and time-of-year information, respectively, to the organism [10]. This information is essential for sleep, temperature regulation, as well as for seasonal reproductive alterations [11–13].

Melatonin also is a powerful antioxidant and anti-apoptotic agent, which due to its direct scavenging of toxic oxygen derivatives and its ability to reduce the formation of reactive oxygen species (ROS) and reactive nitrogen species (RNS) prevents oxidative and nitrosative damage to all macromolecules in all compartments of the cell [14–16]. Mammalian gametes and embryos are particularly vulnerable to oxidative stress [17–19] due to plasma membrane composition, the presence of higher levels of lipids and exposure to dramatic changes in the microenvironment, especially when used in artificial breeding techniques [20,21]. Melatonin has the ability to neutralize damaging ROS and RNS species in these cells, reduce lipid peroxide concentrations and DNA damage, and thereby improve the viability of germ and embryonic cells [22–24]. The role of melatonin in the production and preservation of mammalian gametes and embryos is summarized in this brief review.

2. Melatonin as an antioxidant

Despite of well known hormonal [25], sleep-inducing [26], and chronobiological [27] effects of melatonin, antioxidant properties have also been widely reported. Ianas and colleagues (1991) initially reported and claimed the antioxidant and prooxidant actions of melatonin [28]. Therein they generated free radicals using a combination of luminol and H_2O_2 and used chemiluminescence as an index of free radical production.

The free radical scavenging activity of melatonin was studied in a battery of *in vitro* tests. Wherein they reported that melatonin is devoid of prooxidant actions, at least in the series of tests they performed [29]. Their findings are in line with the previous observations, where they reported that melatonin is an excellent scavenger of trichloromethylperoxyl ($CCl_3O_2^{\bullet}$) free radical [30,31]. Furthermore, they also found that although melatonin reacts with hypochlorous acid (HOCI), though the reaction is slow but it does not directly scavenge the $O_2^{\bullet -}$ free radicals.

Recently several publications have reported the evidence for cardioprotective effects of melatonin via its direct free radical scavenger and its indirect antioxidant activity [32]. Melatonin efficiently interacts with various reactive oxygen and reactive nitrogen species (receptor independent actions) and it also upregulates antioxidant enzymes and down-regulates pro-oxidant enzymes (receptor-dependent actions) [31]. The lipophylic nature of melatonin allows its entry into the cells and subcellular compartments and to cross morphophysiologic barriers. These findings implicate the protective effects of melatonin in cardiac diseases induced by oxidative stress. Its direct free radical scavenging activity [33] and its regulation of gene transcription [34] for antioxidative enzymes has been reported in the literature [35]. The antioxidant properties of melatonin have been extensively studied and summarized its use as a cell protector and as a potential disease-preventing agent [36–39]. Further, melatonin has been proven to be an efficient oxidant scavenger of a variety of radical and non-radical reactants [40]. In addition to this, it has been shown that this neurohormone is able to increase the activity of glutathione peroxidase in rat brain cortex as well as the gene expression for some antioxidant enzymes [41].

3. Melatonin as an oncostatic

Several preclinical and clinical studies have reported the beneficial effects of melatonin against a wide range of tumour [42,43]. Most of these studies focus on hormone-dependant cancers related to disorder of endocrine system included breast, prostate, uterus, cervical uterine, mammary tumours [44], tumour growth, osteosarcoma [45]. Impaired secretion of melatonin has been reported in patients suffering from breast, endometrial, or colorectal cancer [46]. Further increased incidence of breast and colorectal cancer observed in nurses and other night-shift workers suggests a possible correlation between the reduced melatonin secretion and their increased light exposure at night [47,48].

Melatonin exhibits the oncostatic action by its two main properties firstly by *protective effect* such as reversible cellular injury [49] through neurohormone regulation and secondly by *antiproliferative effects*. Moderation of cellular cGMP and cAMP ratios regulates cellular metabolic processes and thus control the production of antioxidants in the cell. Melatonin deficiency results in uncontrolled cAMP synthesis, leading to unregulated oxidative processes and subsequent free radical damage [50]. Alterations of the intracellular redox state play a key role in the effects of high concentrations of melatonin in cancer cells, reducing conditions being associated with a decrease in cell proliferation and oxidative conditions with apoptosis [51]. Melatonin mediates suppression of cAMP levels through melatonergic receptor and thus inhibits uptake of mitogenic substances involves on growth of tumour [52]. It has been demonstrated in various carcinoma cell lines that melatonin increases the activity of glutathione-S transferase enzyme (GST) implicating the role of GST gene on 11q 13 chromosome in cancer [53]. This is supported by the study where melatonin was reported to bound to DNA, chromatin or heterochromatin [10].

Melatonin shows antigonadotropic and antioestrogenic actions in different study module, *in vitro* and *in vivo* on hormone-dependent tumours and cancer cell line [44] as well as antagonised the action of prolactin on human breast cancer cell (HBC) [54]. It selectively neutralised the effects of estrogens on the breast and the local biosynthesis of estrogens from androgens [55]. It has reported that melatonin modulates the enzymes involved in the local synthesis of estrogens by regulating the estrogen receptor expression and transactivation. Further, it has been reported that melatonin activates the immune system [56]. Recently it has been reported