

REVIEW ARTICLE

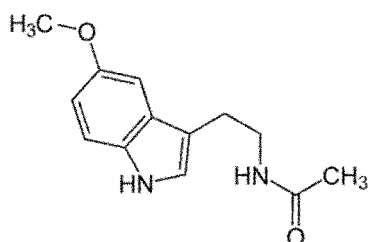
SHORT REVIEW OF REPRODUCTIVE PHYSIOLOGY OF MELATONIN

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INTRODUCTION

Epiphysis Cerebri also known as the Pineal gland produces the hormone melatonin. In 1955 Lerner and Takahashi first developed a so-called bioassay for melatonin determination based on a qualification of frog skin blanching.¹



(Chemical Melatonin Structure)

Now melatonin is considered a hormone (N-acetyl-5 methoxy tryptamine) produced especially at night in pineal gland. Its secretion is stimulated by dark and inhibited by light, which takes place in the pinealocytes, the cellular unit of the pineal gland. Tryptophan is converted to serotonin and finally converted to melatonin, which is an Indole. Melatonin is metabolized to 6-hydroxyl-mel in the liver and the main metabolite excreted is 6-sulphatoxy-mel and this excretion urinary component is helpful in assessing pineal gland function especially in children.²

Melatonin is a ubiquitous natural neurotransmitter involved in numerous aspects of biological and physiological regulation of body functions. The role of endogenous melatonin in circulation rhythm disturbances and sleep disorders is well established. Melatonin has been shown to modify immunity, the stress response, reproductive physiology and also certain aspects of the aging process.

MELATONIN AND HUMAN PUBERTY

Shortly after birth very little melatonin or aMT6s is detectable in body fluids. A robust melatonin rhythm appears around 6 to 8 weeks of life. The plasma concentration increases rapidly there after and reaches a lifetime peak on average at 3 to 5 years old. The increment is much greater at night. Subsequently a steady decrease is seen, reaching mean adult concentration in mid to late teens with the major decline occurring before puberty. Values remain relatively unchanged until 35 to 40 years, and a final decline in amplitude then takes place until low levels

are seen in old age.³ Exceptionally healthy elderly may not show this age related decline.

The precise mechanism controlling the onset of puberty are not fully known yet. The maturing of ovaries and/or testes is triggered by secretion of the hormone FSH and/or LH from the pituitary. In turn, this pituitary function is dependent on GnRH secretion from the hypothalamus, a central control unit of the brain. But, ultimately, we do not know what triggers the function of the hypothalamus with regard to puberty. A possible candidate is melatonin, since there is strong decline of nocturnal concentrations of the hormones particularly before and during puberty. Thus it is hypothesized that high level melatonin inhibits hypothalamus function in humans.⁴

Gonadotropin- releasing Hormone (GnRH) neurons represent the final output neurons in the central control of reproductive system. Gamma-amino butyric acid (GABA), one of the major regulators of GnRH neurons, depolarizes GnRH neurons isolated from adult rats via GABA (A) receptors. The presence of GABA (A) receptors in GnRH neurons has also been demonstrated morphologically. The pineal hormone melatonin is involved in the regulation of reproductive function, including the timing of the luteinizing hormone surge. The Suprachiasmatic nucleus and the GABAergic system in the medial preoptic area are considered as possible sites of the action of melatonin.

Findings indicate that GABA affects the excitability of GnRH neurons in adult rats through GABA (A) receptors, and that melatonin modifies this excitability via melatonin receptors in a sex specific manner.⁵

MELATONIN AS CONTRACEPTIVES

The effect of melatonin on the hypothalamus pituitary axis and therefore the reproductive system have initiated studies aimed at the use of melatonin as an oral contraceptive.⁶ When using high doses of melatonin (75 and 300 mg daily) in combination with norethisterone, no peak in LH secretion was observed during the menstrual cycle. Furthermore, plasma FSH levels remained constant. These circumstances prevented ovulation and the increase in progesterone during luteal phase. The suggested mechanism of action were antigonadotropic effects on the hypothalamus, such as alteration in the hypothalamic

pulsatile GnRH secretion and/or effects on the pituitary release of LH, or even a direct effect on the ovary. Due to melatonin's side effects (especially sleep induction, etc.) this possibility now is seen rather sceptically.⁷

MELATONIN FOR INFERTILITY

Melatonin may be a key factor in the regulation of seasonal variation in gonadal activity. Exposure to bright light, suppressing the concentration of melatonin in circulation, is hypothesized to be useful in treatment of both male and female infertility in couples with abnormal melatonin metabolism.⁸

MELATONIN AS A REGIME FOR CANCER

A long photoperiod results in depressed melatonin secretion during the night. In animals, melatonin inhibits the incidence of chemically induced tumours, which is increased by pineal suppression (long light phase) or pinealectomy.⁹ Pinealectomy stimulates and/or melatonin inhibits the growth and sometimes the metastasis of experimental cancers of the lung, liver, ovary, pituitary, and prostate as well as melanoma and leukaemia.¹⁰

Clinical evidence suggests a role for melatonin in the prevention and even the treatment of Breast cancer.¹¹ The circadian amplitude of melatonin was reduced by more than 50% in patients with Breast cancer vs. patients with nonmalignant breast disease.¹² A high melatonin levels have been found in morning urine samples of breast cancer patients, suggesting circadian disorganization.

Studies suggest three different mechanisms through which melatonin inhibits the growth of breast cancer:

- a) The indirect neuroendocrine mechanism which includes the melatonin down-regulation of the HT-pituitary-reproductive axis and the consequent reduction of circulating level of gonadal estrogens.
- b) Direct melatonin actions at tumour cell level by interacting with the activation of the oestrogen receptor, thus behaving as a selective oestrogen receptor modulator (SERM) and
- c) The regulation the enzymes involved in the biosynthesis of estrogens in peripheral tissues, thus behaving as a selective oestrogen enzyme modulator (SEEM).

As melatonin reduces the activity as expression of aromatase, sulfatase and 17 β -hydroxyl steroid dehydrogenase and increased the activity and expression of oestrogen sulfotransferase, it may protect mammary tissues from excessive estrogenic effect. Thus, a single molecule has both SERM and SEEM properties, one of the main objectives desired for the breast antitumoural drugs.¹³

Since the inhibition of enzymes involved in the biosynthesis of estrogens is currently one of the first therapeutic strategies used against the growth of breast cancer, melatonin modulation of different enzymes involved in the synthesis of steroid hormones makes, collectively, this indolamine an interesting anticancer drug in the prevention and treatment of oestrogen-dependent mammary tumours.¹³

A synergy has been demonstrated between melatonin and all- trans- retinoic acid (ATRA), allowing the use of lower doses of ATRA and thus avoiding its adverse effects.¹⁴

Anisimov *et al*¹⁵ have found that constant treatment with melatonin reduced the incidence and the size of the breast carcinomas as well as lowered the incidence of lung metastasis, but interrupted treatment-promoted, mammary carcinogenesis in transgenic mice. They further observed that the life span of the group receiving interrupted treatment was shorter, however, this outcome could be attributed to the transgenic nature of mice used, but this needs further evaluation.

Melatonin may also be considered to play special role in Prostate. Two-third in patients reduces circadian amplitude of melatonin with prostate cancer as compared with those who have benign prostate disease.¹²

In prostatic carcinoma, melatonin exerts complex interaction with androgen receptors and affects intracellular trafficking; melatonin does not affect cell growth in the absence of dihydrotestosterone.¹⁶

Melatonin is a potent antioxidant agent in preventing testicular Ischemia-Reperfusion injury in rats since they show increased serum inhibin levels and Johnsen's Scores (JS). Melatonin injections have been found to stimulate tumour growth if given in the morning, have no effect when given in mid afternoon and have retarding effect in the evening.^{17,18}

CONCLUSION

Now-a-days pineal gland is small only structurally but functionally it is most important gland releasing a versatile functioning hormone Melatonin. It is not only related to Central Nervous System function but also has strong positive effect in endocrine and reproductive system function. Its pharmacological role in puberty related abnormalities, and role in mechanism of action of pulsatile release of GnRH. Not only in above related roles but its importance is also in cancer therapeutic modalities. Work is going over this hormone to uproot more of its therapeutic functions.

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