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Invited critical review

Melatonin and male reproduction

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ABSTRACT

Melatonin is a neurohormone secreted by the pineal gland whose concentrations in the body are regulated by both the dark–light and seasonal cycles. The reproductive function of seasonal breeding animals is clearly influenced by the circadian variation in melatonin levels. Moreover, a growing body of evidence indicates that melatonin has important effects in the reproduction of some non-seasonal breeding animals. In males, melatonin affects reproductive regulation in three main ways. First, it regulates the secretion of two key neurohormones, GnRH and LH. Second, it regulates testosterone synthesis and testicular maturation. Third, as a potent free radical scavenger that is both lipophilic and hydrophilic, it prevents testicular damage caused by environmental toxins or inflammation. This review summarizes the existing data on the possible biological roles of melatonin in male reproduction. Overall, the literature data indicate that melatonin affects the secretion of both gonadotropins and testosterone while also improving sperm quality. This implies that it has important effects on the regulation of testicular development and male reproduction.

Contents

1. Introduction

The seminiferous tubules and intertubular tissue are compartments of the testis that play essential roles in the production of sperm and testosterone. Various germ cells (spermatogonia, spermatocytes, spermatides, and spermatozoa) are localized in the seminiferous tubules, along with the Sertoli cells. The intertubular tissue consists of blood vessels and diverse cell types, including the Leydig cells responsible for testosterone synthesis [1]. The development of the testes and sperm production is mainly governed by a complex network of signaling processes involving the hypothalamic–pituitary–testicular axis. The Leydig and Sertoli cells are both targets of hormones released by the pituitary gland to regulate testicular development and spermatogenesis [2]. In addition to the established critical roles of hormones produced by the hypothalamus and pituitary gland, there is a growing body of evidence suggesting that the pineal gland is important in testicular development [3,4]. The pineal gland is situated within the brain, adjacent to the superior colliculi and behind the stria medullaris. It is mainly composed of pinealocytes, which produce hormones such as melatonin that regulate physiological processes [5]. Here, we review recent findings concerning melatonin's role in regulating male reproductive physiology.

2. Melatonin secretion and its receptors

The mammalian pineal tissues are morphologically different both across and within species. These differences are thought to be associated with pineal functions and individual responses to environmental factors [6]. According to Vollrath's system of anatomical classification, the human pineal is of type A. Its most abundant cells are pinealocytes,

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which constitute the pineal gland and produce pineal hormones including melatonin [7]. Although some photoreceptors have been found in pineal glands, mammalian pinealocytes are not capable of directly producing hormones in response to light treatment [8]. The indoleamine N-acetyl-5-methoxytryptamine was the first product of the pineal gland to be identified, being isolated from bovine pineal samples in 1958. Because of its role in frog skin melanophores and its similar chemical structure to serotonin, this compound was named melatonin. Extensive subsequent studies demonstrated it to be the most important pineal hormone [9]. The mechanism of melatonin biosynthesis in pinealocytes has been determined by Axelrod [10]. It begins with the uptake of tryptophan from the circulatory system by pinealocytes. The tryptophan is then converted into serotonin via 5-hydroxytryptophan, and serotonin is transformed into melatonin by a two-step process catalyzed by the enzymes N-acetyl transferase (NAT) and hydroxyindole-O-methyl transferase (HIOMT); the NAT-catalyzed step is rate limiting [11]. The genes encoding these enzymes are expressed weakly during the day and strongly during the night, so pineal melatonin secretion exhibits a circadian rhythm [6]. Melatonin can also be synthesized in epithelial cells, bone marrow cells, and lymphocytes, and locally synthesized melatonin is probably important in various physiological processes [12].

Melatonin secretion is mainly regulated by the light/dark cycle, which is controlled by an endogenous clock located in the suprachiasmatic nuclei of the hypothalamus. In mammals, most of the circulating melatonin originates from the pineal gland. This melatonin rapidly reaches all of the body's tissues, passing directly across cell membranes to interact with intracellular receptors due to its high lipid- and water-solubility [13]. However, some functions of melatonin are mediated by interactions with specific membrane-bound receptors [14]. Western blotting, RT-PCR, and in situ hybridization studies on mammalian tissues have identified two high-affinity melatonin receptors (MT1 and MT2) from the G-protein coupled receptor superfamily that are expressed in the brain and peripheral organs [15]. The third known melatonin receptor is named MT3, and was isolated from hamster brain samples; it is not a G-protein coupled receptor and has a comparatively low melatonin affinity [16]. The local production of melatonin throughout the body and the widespread distribution of its receptors suggest that it contributes to the regulation of diverse physiological processes.

3. The roles of melatonin in male reproduction

Interest in the pineal gland's role in regulating the reproductive system has increased substantially in recent years. Melatonin is one of the most important hormones produced by the pineal. In female rats, treatment with melatonin inhibited ovarian development and delayed the onset of puberty [17], while male rats treated with exogenous melatonin exhibited reduced testis size [18,19]. Melatonin receptors have been detected in the human hypothalamus and pituitary, suggesting that melatonin may regulate the production of gonadotropin-releasing hormone (GnRH), FSH, and LH in these tissues [20,21]. It may also regulate testicular development directly by binding to specific receptors expressed in the testes [22].

3.1. The effects of melatonin on the hypothalamus and pituitary

The release of melatonin into the blood is regulated by the dark–light cycle. Because the relative duration of day and night changes with the seasons, the expression of melatonin also varies with the seasonal cycle. The reproductive capacity of seasonal animals varies with the seasonal cycle in a similar fashion, and it has been established that this variation is linked to the seasonal changes in melatonin secretion [23]. The neurohormones produced by the hypothalamus and pituitary are key regulators of the reproductive system, and there is a growing body of evidence suggesting that melatonin's effects on these tissues are responsible for much of its role in regulating reproduction. The pups of female rats treated with melatonin during pregnancy exhibited delayed puberty and abnormal hormonal secretary patterns, suggesting that melatonin is transferred to offspring through maternal milk and influences their subsequent sexual development [24]. It was also found that the delayed onset of puberty following maternal melatonin treatment was caused by reductions in the concentration of LH and prolactin [25]. Melatonin treatment prevented the secretion of FSH and LH in male rats, which would affect their sexual maturation by reducing the stimulation of Sertoli cells by FSH [26]. An in vitro study on fetal rat pituitary cells showed that melatonin can significantly inhibit the induction of LH release by luteinizing hormone releasing hormone (LHRH) [27,28]. The decreased LH secretion from pituitary cells induced by melatonin may be associated with changes in the concentration of Ca^{2+} and cAMP accumulation [29,30]. Increased Ca^{2+} influxes or cAMP concentrations in pituitary cells potentiated the GnRH-induced release of LH but melatonin treatment partially suppressed this response, suggesting that the inhibition of LH release by melatonin may be mediated by reductions in the intracellular concentrations of these second messengers [29]. Another process that helps determine the onset of puberty is the negative feedback effect of testosterone on gonadotropin secretion. Melatonin treatment enhanced this effect, delaying sexual maturation in male rats [31].

The hypothalamic neurons in the suprachiasmatic nuclei (SCN) and the neurons that secrete gonadotropin-releasing hormone (GnRH) are the main targets of melatonin in the hypothalamus [32]. However, melatonin receptors are also expressed in the pars tuberalis and pars distalis regions of the anterior pituitary [20]. The reproductive actions mediated by the melatonin receptors in the hypothalamic neurons and anterior pituitary are different. The phase-changing effects on the circadian rhythms are mainly controlled by melatonin receptors in the SCN. Genetic inactivation of both MT1 and MT2 receptors in mice can cause changes in the circadian rhythm [33]. However, the roles of melatonin receptors in the anterior pituitary are time-dependent due to the postnatal decline in the abundance of melatonin receptors in the par distalis [21]. The presence of melatonin receptors in the hypothalamus and pituitary is consistent with the hypothesis that melatonin's influence on reproduction is due to its effects on the secretion of GnRH and pituitary hormones. The implantation of melatonin-containing pellets into the GnRH neuronal system of the hypothalamus reduced testis weight by up to 60% in male mice compared to implant-free mice [34]. Although melatonin increases the number of GnRH-secreting cells, it does not significantly affect their size or morphology [34]. These results indicate that melatonin's effects in the hypothalamus stem from suppressing the release of GnRH rather than its synthesis. Progressive treatment of male mice with melatonin over 10 days caused significant reductions in testicular and seminal vesicle mass, and also reduced or completely suppressed sperm production [35]. Subsequent treatment with exogenous gonadotropins reversed these changes in the mass of the testes and accessory sex organs [36]. The inhibition of GnRH release by melatonin was confirmed by in vitro studies on immortalized GnRH-secreting neurons [37].

Recent findings show that GnRH synthesis and release can be regulated by a neuropeptide named gonadotropin-inhibitory hormone (GnIH), which was first discovered in quails by a Japanese group in 2000 [38]. GnIH analogues have since been identified in diverse avian species and mammals [39]. The main function of GnIH in animal physiology is to inhibit GnRH synthesis and release by acting on the GnRH neurons [40]. It may also target the anterior pituitary, where the GnIH-receptor is widely distributed [41]. The expression of LH-b and FSH-b was down-regulated in sheep treated with GnIH [39]; similarly, cows treated with GnIH exhibited a reduced LH pulse frequency [42]. The synthesis and release of GnIH in the hypothalamus are regulated by multiple factors including the photoperiod, stress, and internal signals [39]. Melatonin may have profound effects on one or more of these factors. In photoperiodic animals, melatonin is mainly synthesized by the pineal gland and eyes. Quails that have undergone pinealectomy

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