Received: 30 Jan, 2024 | Revised: 17 March 2024 | Accepted: 27 March 2024

MANUSCRIPT ID: CoAS_V1SP1_14

REVIEW

Chronicle of Aquatic Science

Advances in Melatonin Research – A Review

A. R. Jumnake*[1] | V. R. Patodkar[1] | N. E. Gavali[1] | V. M. Sardar[1] | P. V. Mehere[1]

[1]Department of Veterinary Physiology, K. N. P. Collage of Veterinary Science Shirwal, Satara, MAFSU, Nagpur, Maharashtra, India.

Correspondence
A. R. Jumnake, K. N. P. Collage of Veterinary Science Shirwal, Satara, MAFSU, Nagpur, Maharashtra, India.
Email: aishwaryajumnake@gmail.com

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Authors Contribution

All authors listed have made a substantial, direct, and intellectual contribution to the work, and approved it for publication.

Abstract

The chemical known as melatonin, N-acetyl-5-methoxytryptamine, is widely dispersed and very versatile in its functional aspects. The processes involving the retina and biological clock that regulate the pineal gland's circadian melatonin production are quickly being discovered, and the mechanisms governing its synthesis within the gland have been thoroughly studied. According to the research, melatonin, both endogenous and exogenous, plays a significant role in promoting physiological and molecular adaptations in domestic animals and wildlife. Seasonally polyestrous animals have been the subject of substantial melatonin research. Herds of animals housed in photoperiodic aberrations have their circannual cycles corrected by supplementation procedures. One of its defining characteristics is the range of techniques melatonin uses to alter cell physiology and molecular biology. However, the antioxidant and immunostimulatory properties of melatonin may be able to mitigate these effects. During their production cycle, livestock undergo several metabolic and physiological adaptation processes that may impair their immune system and result in chronic sickness, weight loss, or decreased productivity. Melatonin has an impact on the heart and blood vessels. It can vasodilate or vasoconstrictor numerous systemic arteries, depending on the kind and location of its receptors. This modulates the animal's total nutrient partitioning through vascular resistance. The physiological, cellular, and molecular impacts of melatonin on the well-being and illnesses of domesticated food animals are the main topics of this review, along with recent developments in the subject.

KEYWORDS

Antioxidant; circadian rhythms; reproductive physiology; functional element; immune function

INTRODUCTION

The pineal gland is a small endocrine organ located in the epithalamus, attached to the roof of the third ventricle, and it is involved in the regulation of various physiological functions, including the sleep-wake cycle and the secretion of melatonin. Melatonin is also called as 3rd eye or heavenly eye because of the belief that the pineal gland has a special significance beyond its recognized physiological functions. This symbolic representation is not a scientific designation but reflects different traditions' historical and cultural perspectives. René Descartes called this region of the brain "the seat of our soul" in the 17th century because he believed that it is where our thoughts originate. McCord and Allen reported in 1917 that bovine pineal extracts were effective at lightening frog skin. Melatonin was named after Lerner et al., who identified N-acetyl-5-methoxytryptamine, Dermatologist Aaron Lerner isolated melatonin, a secretory substance, from the pineal gland of cows in 1958. Most studies conducted after melatonin was discovered in 1958 (Aeron) aimed at comprehending how melatonin functions in the reproductive physiology of photosensitive seasonal breeding mammals (Reiter, Chemineau, Ronayne). Nighttime elevation of melatonin is recognized as a highly conserved feature in vertebrate species, and it plays a major role in circadian rhythms and seasonality of reproduction.

Activation

In mammals, 95% of pinealocytes release melatonin (Moller et al., 2016). Higher vertebrates have retinas, while cold-blooded vertebrates have photosensitivity. (ex-humans and reptiles). Current light-dark cycles are the primary function. (Goldman et al., 1993).

One of the organs that receives neural information from the SCN is the pineal gland. As a result, the paraventricular nuclei of the hypothalamus receive axons from the pacemaker neurons in the central clock, among other locations. These are preganglionic sympathetic neurons, whose fibers descend through the brain stem most likely without making synaptic contact with other cells until they reach the upper thoracic cord's intermediate lateral cell column (Karasek et al.,1983). After making a final connection with these cells, the preganglionic axons leave the spinal cord and ascend the sympathetic chain to the superior cervical ganglia. When blood arteries lead to the pineal gland, postganglionic neuron axons follow. (King et al.,1985) Within the pineal gland, next to the postganglionic fibers, are the pinealocytes, the gland's melatonin-producing cells. (Maronde et al.,2011). In the dark, postganglionic terminals near the pinealocytes release norepinephrine in response to neural impulses from the SCN. Pineal melatonin generation and release increase during the nighttime due to a series of chemical events triggered by the catecholamine's predominant effect on the usual β-adrenergic receptors on pinealocyte membranes (Vaughan et al.,1976, Tricoire et al.,2002). The link between the pineal gland, the SCN, the peripheral nervous system, and the ipRGCs is depicted diagrammatically.

Signaling

It appears that different tissues and cell types have diverse melatonin receptor signal transduction pathways (Von Gall et al., 2002; Witt-Enderby et al., 2003) Using recombinant melatonin receptors, it has been shown that the MT1 melatonin receptor is connected to many G proteins that mediate phospholipase C beta activation and adenylyl cyclase inhibition. Therefore, activation of the MT1 receptor leads to the activation of multiple G proteins, including Gia2, Gia3, and Gaq (Brydon et

al., 1999), as well as Gas, Gaz, and Ga16 (Ho et al., 2001; Chan et al., 2002). In certain of these systems, melatonin suppresses the cAMP signal transduction cascade (Niles and Hashemi, 1990; Brydon et al., 1999). Among these include decreases in protein kinase A activity and phosphorylation of nuclear factor CREB (cAMP response element binding protein) (McNulty et al., 1994). (Morgan et al., 1994). According to Morgan et al. (1994), the main effect of MT1 receptor activation in hypophyseal PT is the reduction of cAMP accumulation. However, in human neuroblastoma SH-SY5Y cells (Schuster et al., 2005) and COS-7 cells (Chan et al., 2002) transfected with cloned MT1 receptors, melatonin raises cAMP. Although the exact mechanism is still unknown, Gi or Gs proteins did not mediate this stimulatory impact. According to theories put forth by Chan et al. (2002) and Schuster et al. (2005), it has to do with the activation of c-Jun N-terminal kinase and the calcium-calmodulin signal transduction pathway.
The MT2 receptor inhibits adenylyl cyclase's inhibition of the soluble guanylyl cyclase pathway and links to multiple signal transduction pathways, including those that generate phosphoinositide (Boutin et al., 2005). Studies have demonstrated that in NIH3T3 cells transfected with human MT2 melatonin receptors, high melatonin concentrations can reduce cAMP production (Reppert et al., 1995; Jones et al., 2000). Moreover, it seems that MT2 receptors cause an increase in PKC activity, which mediates the phase-shifting effects of melatonin in slices from the rat SCN (McArthur et al., 1997; Hunt et al., 2001).

Synthesis

Tryptophan is a starting point for the manufacture of melatonin. After tryptophan is hydroxylased to 5-hydroxytryptophan, it is converted to N-acetylserotonin (NAS) by arylalkylamine N-acetyltransferase (AANAT), which is subsequently converted to melatonin by acetylserotonin O-methyltransferase (ASMT), formerly known as hydroxy-indole-O-methyltransferase (HIOMT). The neurological and endocrine mechanisms that govern the quantity, duration, and time of melatonin production also control the three enzymes above (Afeche et al.,2008)

Metabolism

Previous research suggested that virtually solely the hepatic P450 monooxygenases catabolized melatonin, which led to the conjugation of the resultant 6-hydroxymelatonin to produce 6-sulfatoxymelatonin, the primary urine metabolite. This might apply to tissue melatonin, but it might not apply to the hormone that is in circulationThe central nervous system is particularly prone to oxidative pyrrole-ring cleavage, and subsequent injection of melatonin into the cisterna magna did not reveal the presence of 6-hydroxy melatonin (Hirata et al., 1974). Given that the pineal recess distributes significantly more melatonin into the cerebrospinal fluid than it does into the bloodstream, this may be particularly significant (Tricoire et al., 2002). The main cleavage product is N1-acetyl-N2-formyl-5-methoxykynuramine. Unexpectedly, AFMK is the result of many enzymatic (myeloperoxidase, indoleamine 2,3-dioxygenase), pseudoenzymatic (oxoferryl hemoglobin, hemin), photocatalytic, or free-radical processes (Hardeland, 2005). Recent estimates (Ferry et al., 2005) place the amount of catabolism that results from pyrrole-ring cleavage at about one-third; however, in certain tissues, this ratio may be significantly higher. Other oxidative catabolites include a 2-hydroxylated analog that does not cyclize but instead becomes an indolinone, and cyclic 3-hydroxy melatonin (c3OHM), which can similarly be converted to AFMK (Hardeland, 2005). Other hydroxylated or nitrosated metabolites have

been discovered, however these appear to be present only in trace amounts. Additionally, AFMK and AMK interact with reactive oxygen and nitrogen species to produce metabolites (Hardeland 2005). The brain has evidence of cytochrome P450 subforms. They either produce 6-hydroxy melatonin, which is mostly sulfated already in the central nervous system, or demethylate melatonin to acetylserotonin. At the very least, the pineal gland and retina deacetylate melatonin to 5-methoxytryptamine. N1 -acetyl-N2 -formyl-5-methoxykynuramine is the result of the combination of indoleamine 2,3-dioxygenase, myeloperoxidase, pyrrole-ring cleavage, and various non-enzymatic oxidants. Because it is a scavenger of reactive oxygen and nitrogen species, mitochondrial modulator, downregulation of cyclooxygenase-2, inhibitor of cyclooxygenase, and inhibitor of neural and inducible NO synthases, its product, N1-acetyl-5-methoxykynuramine, is significant. 3-acetamidomethyl-6-methoxycinnolinone is a nitrosated kynuramine metabolite that does not re-donate NO or the amount of melatonin generated, in contrast to other nitrosated aromates (Hardeland et al., 2010).

ADVANCEMENT IN MELATONIN RESEARCH

MELATONIN IN REPRODUCTIVE PHYSIOLOGY

To increase the productivity of this species, sheep producers currently employ reproductive control techniques that are mostly focused on females (hormonal treatments based on melatonin, photoperiod programs, and progestagens). Rams receive very little attention since ewes are frequently singled out when it comes to infertility, or the inability of a herd to reproduce, and because rams' ability to procreate is too frequently taken for granted (Colas et al). According to Augas et al., the ram plays a crucial role in reproductive outcomes since it affects both prolificity and fertility (also depending on the ewe's capacities). Research has successfully demonstrated that several melatonin treatments affect the parameters associated with ram reproductive activity. These investigations have mostly concentrated on seasonal breeds in temperate and Mediterranean climates, where a natural drop in performance was observed to be accompanied by an improvement in semen quality. Nevertheless, no research has shown that ewes' prolificity and fertility under mating settings can correspond with the melatonin-induced increases in indirect indicators of reproductive ability (Tariq et al., 2012). Additionally, the selection of genetically better animals for production and reproduction depends mostly on data on the body size and testicular features of different breeds at constant age. (Koyuncu et al.,2005) the effects of melatonin on semen quality and also the testicular growth in rams breed, a tropical nation where animals are nearly always in a sexual season and are not at all susceptible to photoperiodic fluctuations. While the testicles' weight and anteroposterior diameter decreased (because of the onset of a freshness period), melatonin medication enhanced most sperm metrics as compared to the control group. Melatonin, when compared to the control, resulted in a considerable improvement in the mass and individual motility of spermatozoa, as well as a very low level of aberrant spermatozoa survival. However, because motility is necessary for sperm to migrate in the female genital tract, it is a significant metric of semen preservation that is used to assess the impact of storage. (Assani et al.,2023) The chemical messenger that allows seasonal animals to recognize changes in day length is melatonin, which is produced by the pineal gland (Chemineau et al., 2008; Rahawy et al., 2017). The melatonin level changes daily due to a translation of the external photoperiodic signal by a neuroendocrine system. according to Rosa et al., (2012) and Sarlos et al. (2013), slow-release implants containing exogenous melatonin may be a useful tool for controlling the rhythm of reproduction. It is possible to counteract the

"long-day effect" on the ram during the nonbreeding season by using melatonin implants (Rosa et al.,2012) The hormone testosterone has a fundamental impact on the reproductive behavior and secondary sexual features of rams (Hafez and Hafez, 2013). Awassi rams treated with melatonin implants showed improvements in their testosterone levels and sexual behavior in various seasons The treatment group's springtime ejaculation was significantly greater (P 0.05) than the control group's. During the summer, the testosterone levels in the treated group were significantly (P 0.05) higher than those in the control group. (Shammary, et al.,2023) that during the reproductive seasons, melatonin increases the mRNA expression of melatonin receptors and melatonin-forming enzymes in growing horse follicles.

Mares' reproductive activity exhibits a seasonal pattern, with a spring and summer strong incidence of ovulations linked to an increasing photoperiod. Melatonin, which the pineal gland secretes, is responsible for the photoperiodic regulation of reproductive function. Melatonin suppresses ovulatory activity by acting through the hypothalamic-pituitary axis. the mRNA expression of gonadotropin receptors (Fshr and Lhr), melatonin receptors (Mt1 and Mt2), melatonin-synthetizing enzymes (Asmt and Aanat), and melatonin during the different seasons in developing follicles (small—<20 mm, medium—20 to 35 mm, and large—>35 mm) from five mares raised in natural photoperiods. Melatonin levels in growing follicles increased in the spring and summer, coinciding with an increase in the mRNA expression of genes related to gonadotropin and melatonin receptors. There was a noticeable increase in the overall count of big follicles, or putative ovulatory follicles, during the spring and summer. According to our findings, throughout the reproductive stage, melatonin promotes the mRNA expression of melatonin-forming enzymes and melatonin receptors in developing mare follicles (Coelho et al., 2023). After receiving a single dosage of melatonin, the crossbred buffaloes demonstrated ($p < 0.05$) enhanced estrus response, ovulation occurrence, and follicular enlargement in comparison to the control groups. The content of the milk was unaffected by the melatonin administration (Cosso et al 2021). Furthermore, melatonin administration enhanced the levels of IgM in treated buffaloes as well as milk parameters such as MUN, milk protein, and somatic cell count (Coelho et al.,2023).

A neurohormone known for its involvement in many biological processes, melatonin also helps animals with seasonal breeding cycles regain their cyclicity. Different types of melatonin have become more widely accepted in many species, especially in summer anestrous buffaloes. In crossbred buffaloes, melatonin administration at a single dosage has improved ($p<0.05$) the occurrence of ovulation, estrus response, and follicular enlargement. Both buffalo groups treated with melatonin exhibited higher rates of pregnancy than the control group. Serum IgM levels increased after melatonin infusion. Following the administration of melatonin, the somatic cell count in buffalo milk decreased ($p < 0.05$). (Abdulaiti, 2023) Following CIDR application and melatonin treatment, a growing proportion of ovulatory follicles in nursing buffaloes and heifers (Al-Hamedawi and Planski). Protein and lactose levels have increased due to melatonin. (Cosso and Wu) Melatonin can enhance the body's antioxidant level (Biancatelli et al.,2020)and control cytokine synthesis (Afeche et al.,2008), which in turn can control immunological function.

When the dry-off period began, dairy cows who got melatonin therapy had superior reproductive success throughout the warm season. Treatment reduced the incidence of repeat breeding syndrome and the number of pregnancies lost in the first trimester of gestation. Additionally, there was no negative

impact of melatonin administration on the subsequent lactation, even though the animals' plasma prolactin concentrations decreased during the dry-off phase before rising to normal in the early postpartum phase. (Ispierto Garcia et al., 2013) Additionally, melatonin has been associated with increased embryo survival in vitro during the IVM or IVF treatment in cattle (Papis et al. 2007; Takada et al. 2012). Although there are many contributing factors to repeat breeding, ovarian function, and oocyte quality at AI most likely play a role in a cow's fertility. Therefore, melatonin from outside sources may increase oocyte viability. In certain animals, such as rats, the frequency of spontaneous miscarriages increases after pinealectomy. According to Tamura et al. (2008a, 2008b) state that as a result of these activities and the reduction of prostaglandin synthesis melatonin appears to be the best option to improve the health of the embryo and fetus.

MELATONIN AND GUT-MICROBES

In addition to controlling the intestine's biological rhythms for immunological, absorptive, and digestive processes, gut hormones also affect the host due to their interactions with intestinal microbes. Unknown is the relationship between ruminal hormones and the ruminal ecology.

There were notable differences between the GIT levels of different species, but the amount did not differ much between individual segments of the same species. (Bubenik, G.A 1997)

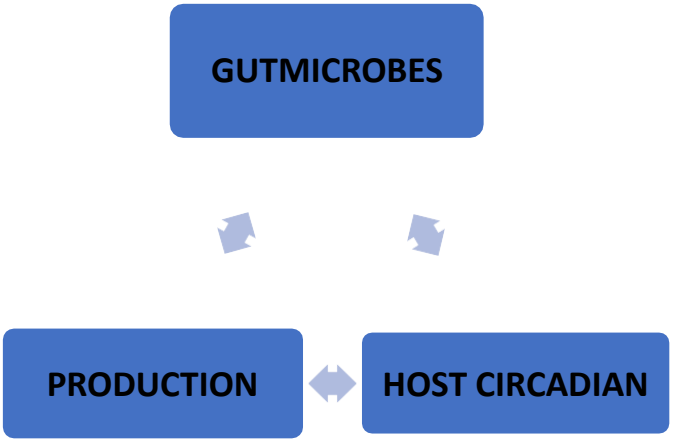

Figure 1: Cyclical Nature of Host and Melatonin

Melatonin is present in rumen fluid, albeit its concentration varies throughout the day. Furthermore, 9% of all rumen bacterial operational taxonomic units (OTUs) have a proportionate abundance that shows a circadian rhythm. Ruminal fluid included GH and PRL, but there was no discernible daily pattern in their concentrations. Ruminal melatonin had significant in vivo connections with the following families: Muribaculaceae, Succinivibrionaceae, Veillonellaceae, and Prevotellaceae. Melatonin therapy had a substantial effect on these families in vitro, as it decreased the relative abundance of Succinivibrionaceae and Veillonellaceae, and increased the relative abundance of Prevotellaceae and Muribaculaceae. When taken as a whole, ruminal microorganisms seem to keep a circadian rhythm linked to melatonin profiles. Therefore, evidence points to a potential function for melatonin generation in the rumen in host-microbe interactions in ruminant animals. (Jialiang Ouyang and associates, 2021). Ma et al. (16) demonstrated a robust correlation among mucosal immune cells, gut microbiota, and MLT. According to Paulose and Cassone (Paulose et al., 2016) and Paulose et al. (Paulose et al., 2006), MLT affects Enterobacter aerogenes and other gut bacteria in people on a circadian basis. Furthermore,

Zhu et al. (2018) found that in the guts of colitis-affected animals, MLT therapy increased Firmicutes and decreased Bacteroidetes relative abundance, which went from 58.93 to 41.63%. Melatonin is expected to play a critical role in mediating ruminal microbes and their metabolic pathway, as these diurnal cycle bacteria were responsive to melatonin in vitro and closely associated to melatonin in vivo. Proteobacteria, Bacteroidetes, and Firmicutes—the three major phyla—showed a connection between melatonin and their in vivo rhythmic oscillation.

Nighttime serum melatonin concentrations are greater, which supports the idea that melatonin is a necessary hormone that controls biological cycles. While the pineal gland does not produce as much melatonin when there is light present, it does produce it in reaction to darkness in the surroundings. (Armstrong and others, 1989) It is well known that MLT can have a deleterious effect on Gram-negative bacteria.

In addition to being crucial for controlling the host's circadian rhythm, MLT also controls the gut by influencing the circadian rhythms and metabolism of the microbiota. Paulose and Cassone shown that Melatonin could affect Enterobacter aerogenes and that this hormone is involved in regulating the circadian cycle of E. oncogenes. According to Ma et al. MLT can affect gut microorganisms by influencing cytokines produced by the intestinal epithelium, such as IFN-γ. Furthermore, O'Keeffe et al., showed that MLT can modify intestinal microbial metabolism in mice by activating NF-κB. Moreover, mice given a high-fat diet were able to restore the disturbed diurnal cycles of the gut microflora with the administration of exogenous MLT, according to Yin.

MELATONIN AS FUNCTIONAL ELEMENT

The most notable characteristic of melatonin that has emerged as a result is its strong cytoprotective action on various levels of damaged cells, both at physiological and pharmaceutical concentration (Slominski, A. et al., 2008). In clinical dermatology, it is preferable to apply exogenous melatonin topically rather than orally because the latter arrives in the blood at relatively low levels because of significant liver first-pass degradation, which restricts skin availability. (Fischer et al.,) Melatonin's unique lipophilic chemical composition allows it to enter the stratum corneum and form a depot there (Fischer et al.,2004). Therefore, it is expected that endogenous intracutaneous melatonin production in combination with topically applied exogenous melatonin will provide the most effective defense mechanism against cutaneous photodamage (Fischer et al., 2006) and many other pathologic conditions that cause oxidative stress (e.g., chronic skin inflammation, such as atopic dermatitis) (Schallreuter et al., 2008). Since several decades ago, there have been indications that melatonin controls the growth and coloration of hair according to the season (Slominski et al.,). For example, in some mammalian species, melatonin influences the growth and frequency of pelage cycling, seasonal molting, and wool and cashmere production. It can also alter the coat's color.

The innovative melatonin and essential oil combination in dietary supplements and topical application shows promising results for treating a variety of pet dysfunctions, such as anxiety and stress, insomnia, alopecia, and problems with hair growth. discovered that giving dogs with Leishmaniosis a topical melatonin + EOs cream every two days for four to five weeks considerably reduced their affectation, lowering dermatitis and skin irritation. Erosion wounds therefore became better with time.(Domingo Ruiz-Cano et al., 2022)

NAT enzymatically acetylates melatonin and 2-oxo melatonin, resulting in the production of hypnotic acetyl metabolites, such as carbo2. The parent substance of these metabolites is melatonin. Treating sleep disorders may require medication since the lack of NAT enzymes in the pineal gland may be the cause of insomnia and other sleep disorders. Giving hypnotic acetyl metabolites of melatonin or its synthetic analogs is one possible treatment for insomnia patients (Fourtillan et al., 2002).

MELATONIN AS ANTIOXIDANT

In unicellular organisms, their early roles include that of an antioxidant and a free radical scavenger (Reiter et al., 2013). Increased levels of cellular glutathione peroxidase (GPx) and longevity are two benefits of the anti-aging effect (NAS (Suzen et al.,2018). When infertile mammals receive melatonin therapy, their intra-follicular melatonin concentrations rise, intra-follicular oxidative damage decreases, and their rates of conception and pregnancy rise. Infertile mammals with luteal phase deficiency that get melatonin therapy also exhibit improved corpus luteum progesterone production. A potential treatment for infertility that improves oocyte quality and luteal function may be melatonin therapy (Tamura et al.,2013)

Melatonin is another highly strong antioxidant, possessing an antioxidant capacity several times more than that of conventional antioxidant compounds such as ascorbic acid, glutathione (GSH), and vitamin E. Through both in vitro and in vivo experiments, Reiter's group and others have comprehensively demonstrated the scavenging effect of melatonin against reactive oxygen species (ROS) and reactive nitrogen species (RNS). It has been demonstrated that melatonin's antioxidant effect is enhanced by the synthesis of several of its reaction products, including cyclic-3-hydroxy melatonin, N1-acetyl-N2-formyl-5-methoxykynuramine (AFMK), and N1-acetyl-5-methoxykynuramine (AMK), both in vitro and in vivo (Galano et al., 2013). Additionally, animal tissues produce more antioxidant enzymes in response to oxidative stress and exposure to harmful substances when melatonin is present. Superoxide dismutases (SOD), catalases, GSH peroxidases, GSH transferases, and GSH synthases are among the enzymes that melatonin up-regulates as a result, to aid them in handling potentially stressful conditions. To regulate the redox network, melatonin can generally modify the levels of ROS/RNS by (i) directly scavenging them in a receptor-independent manner and (ii) directing the generation of antioxidant enzymes in a receptor-dependent manner (Arnao et al.,)

In several Parkinson's disease models (dopamine auto-oxidation, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, and 6-hydroxydopamine), melatonin has shown prophylactic effects on reducing the toxicity of the amyloid β protein, ischemia-reperfusion injury, protection against glutamate excitotoxicity, and reduction of neural damage from porphyria, hyperbaric hyperoxia, and various neural toxins. Since endogenous melatonin levels decrease noticeably with age, our data imply that the loss of this antioxidant may increase the occurrence or severity of various neurological problems linked with aging (Reiter et al., 1998)

MELATONIN IN ROUTINE

We have made great strides in understanding the functional sensitivity of MT1 and MT2 receptors, which are crucial for two of the SCN's two hypothesized primary functions, even though the SCN and melatonin release are unquestionably in charge of controlling circadian and other sleep-related activity: sleep induction phase shifting and sleep promotion (Dubocovich et al ., 2007) The disturbance of the circadian system due to external factors like shift work or jet lag, or internal factors like age or blindness, can

result in a variety of health issues. The circadian system regulates a multitude of physiological and behavioral activities. At first appearance, the effectiveness of treatments involving the external application of melatonin as a chronobiotic medicine to treat desynchronization and circadian disorders seems to support the hypothesis that melatonin plays a crucial role in the synchronization of the circadian system. Melatonin is one ingredient in a concoction of synchronizing agents rather than the master of internal synchronization. (Pfeffer et al.,2018)

Numerous studies show that it acts through G protein-coupled membrane MT1 or MT2 receptors to physiologically influence numerous regions of the central nervous system, including the hippocampus, prefrontal cortex, dopaminergic pathways, and cerebellum. (Pandi-Perumal et al.,2008) Melatonin's physiological effects in the SCN and hippocampus, along with the presence of MT1 and MT2 receptors in these regions, suggest that these receptors are involved in sleep regulation, circadian rhythms, and maybe memory consolidation.

MELATONIN AND MALERIA

Melatonin facilitates the phospholipase C-inositol 1,4,5-trisphosphate (PLC-IP3) signaling cascade, which in turn synchronizes the intraerythrocytic cycle of the parasite. Indole scaffold-containing compounds inhibit blood-stage malaria parasite growth in vitro, suggesting that this family of chemicals may one day become antiplasmodial medications, sulfenylindoles have the potential to act as antimalarials against parasites that are both vulnerable and resistant to chloroquine, much like the host hormone melatonin. (Mallaupoma et al., 2022). In the ring and early trophozoites, P. falciparum displays stage-specific spontaneous Calcium (Ca^{2+}) oscillations; the latter was crucial for the growth of the parasite. In this work, we demonstrate that the selective melatonin receptor antagonist luzindole (LZ) reduces the proliferation of parasites. Studies on the growth and morphology of P. falciparum treated with LZ showed that the drug significantly hampered intraerythrocytic maturation, which ultimately to the death of the parasite. The addition of LZ at the ring stage prevented the parasite from developing further, while LZ injected at the trophozoite stage prevented the formation of early to late schizonts. LZ treatment did not affect early trophozoites but eliminated Ca^{2+} oscillation in the ring forms, according to live-cell Ca^{2+} imaging. The intricate interaction between the cAMP and IP3-Ca^{2+} signaling pathways plays a role in P. falciparum's intraerythrocytic development (Furuyama et al.,2014).

DIABETES AND MELATONIN

The islets of Langerhans, which are in charge of secreting insulin, contain the isoforms MT1 and MT2 (Peschke et al., 2013) Furthermore, the CNS and many brain and spinal cord regions and other peripheral tissues, such as the liver and adipose tissue, also express melatonin receptors, which help to regulate metabolic processes. There is evidence linking circadian dysrhythmia-linked diabetes mellitus to melatonin, a pineal hormone with anti-inflammatory and antioxidative qualities. In the pathophysiology of type 2 diabetes (T2D), reduced melatonin levels and a functional relationship between melatonin and insulin are involved. Furthermore, uncommon variations in melatonin receptor 1b (MTNR1B) have been linked to a higher risk of type 2 diabetes and reduced glucose tolerance, according to genomic studies. Furthermore, exogenous melatonin therapy has demonstrated a strong beneficial effect in reducing diabetes and its associated problems in cell lines, rodent models, and diabetic patients. This emphasizes melatonin's function in maintaining glucose homeostasis. On the other hand, reports about the effects of supplementing with melatonin are similarly inconsistent.

Investigating whether melatonin can be administered from bench to bedside for the treatment of diabetes is therefore crucial. (Patel et al., 2022) Melatonin's strong antioxidant and nephroprotective properties make it appear advantageous for the treatment of diabetes. The enhancement of glutathione metabolism enzyme activities brought on by indole may play a role in the antioxidant properties of melatonin in diabetic circumstances. It might demonstrate the mutually beneficial effects of insulin and melatonin, which would provide veterinarians with fresh insight into how to treat liver complications in addition to diabetes (Hajam et al.,2019). When compared to the individual therapies, co-administration of melatonin and insulin led to greater decreases in the circulation levels of interleukin (IL)-1β, IL-6, tumor necrosis factor-α, and tumor growth factor-β1, but increased levels of IL-10. In diabetic rats, there was a considerable increase in the expression of both the MT1 and MT2 melatonin receptor genes. Treatment with insulin or melatonin, alone or in combination, markedly improved the renal cortex's relative expression of both melatonin receptors. Insulin and exogenous melatonin coadministration reversed many of the negative effects of type 1 diabetes on rats' kidney function. (Hajam et al., 2022).

HEART AND MELATONIN

MT1 and MT2 receptors found in arteries and the heart (Masana and Pang et al., 2002) the minimal toxicity and great effectiveness of melatonin in reducing ischemia/reperfusion damage has been found (Reiter et al.,2003). The SCN affects the autonomic output of the cardiovascular system. In hypertensive patients, restoring the SCN's normal function may enhance the autonomic control of blood pressure (BP) (Scheer and Sly). Melatonin taken repeatedly before bedtime dramatically decreased nocturnal blood pressure in patients with essential hypertension (Scheer et al.,2004). Partially responsible for the activation of eNOS and vasorelaxation of MAs, melatonin stimulates the BKCa channels on mesenteric arterial myocytes by direct (via the cell membrane) and indirect (via the MT1/MT2 receptors) means. Zhao and colleagues, 2017 Melatonin receptor activation has complex effects on vascular function, causing vasodilation in some vasculatures and constriction in others. According to studies, melatonin, for instance, causes vasodilation in some arteries (Doolen et al., 1998), such as the aorta, the pulmonary and umbilical vascular bed, and mesenteric arteries (MAs) (Thakor et al., 2010), but causes vasoconstriction in other arteries (Viswanathan et al., 1997), such as cerebral arteries (Geary et al., 1998), the renal vascular bed (Tunstall et al., 2011), and coronary vessels (Geary et al., 1998). These contradictory effects may be caused by melatonin binding to two different receptors that are distributed differently on various circulatory beds (Doolen et al. 1998). Numerous investigations have connected MT1 receptor activation to cAMP decrease and phosphatidylinositol-4,5-bisphosphate hydrolysis, both of which impede vasodilation or vasoconstriction (Paulis & Simko 2007). The activation of MT2 receptors on endothelial cells (ECs) may lead to increased production of nitric oxide (NO) and endothelium-dependent vasodilation (Anwar et al. 2001, Paulis & Simko 2007, Reiter et al. 2009).

MELATONIN AND IMMUNISATION

Melatonin is an amino acid-derived hormone that is an immunostimulatory, anti-apoptotic, antioxidant, and regulates immunological responses—more especially, it strengthens the Th-1 immune system. (Esquifino et al.,2004). Researchers have observed that administering melatonin to pregnant lambs as a vaccine adjuvant greatly enhanced the immune responses to the vaccine antigen.(Regodón et al.,2012). Enhancing the immune response to vaccination and the generation of antibodies in pregnant women can improve the quality of their colostrum, which will benefit their offspring's health; hence, this

potential use warrants more research. It's interesting to note that, in comparison to nonimplanted ewes, ewes implanted with 18 or 36 mg of melatonin 40 days before lambing showed higher IgG concentrations in colostrum and a lower somatic cell count in the lactation that followed (Canto et al.,2022). Melatonin has been extensively experimented with in dairy cows as a treatment to improve the success of reproduction in cows who are under heat stress (Abdelnaby et al.,2021). Melatonin has typically shown promise in reducing the number of days open and the repeat breeding syndrome in heat-stressed dairy cows (Garcia-Ispierto et al., 2013). The use of melatonin as a therapy for common stressors in cattle is, however, a subject of limited investigation. Strong immunomodulators and antioxidant melatonin are essential for coordinating the body's internal response to internal light stimulation with the outside world. Green and blue monochromatic light (560–480 nm) reduced the inflammatory response and shielded lymphoid tissues from oxidative stress, but red monochromatic light (660 nm) maintained the inflammatory response and encouraged the growth of dangerous bacteria. By encouraging the proliferation of B and T lymphocytes, green monochromatic light (560 nm) raised blood melatonin levels and strengthened the humoral and cellular immune response (Horodincu et al., 2023) The growth performance and antioxidant status of stressed birds were both improved by a 60 mg melatonin treatment. Supplementing with melatonin mitigated the dexamethasone-induced effects on IL-6 and IL-10. The treatment of melatonin decreased AST, ALT, and ALP activity as well as the heterophil. (Fathi et al, 2023) This implies that giving broiler chicks melatonin may help them minimize the negative consequences of stress.

MELATONIN AND ANTI-CANCEROUS EFFECTS

Physiological and pharmacologic dosages of the pineal hormone melatonin have shown chemopreventive, oncostatin, and tumor-inhibitory effects in a variety of in vitro and in vivo experimental models of neoplasia (Jung et al.,2006) Melatonin directly inhibits MMP7 expression, which therefore reduces chondrosarcoma cell migration, proliferation, and anoikis resistance. Melatonin increased the expression of miR-520f-3p in human chondrosarcoma tissue samples, which therefore reduced the synthesis of MMP7. Pharmacological suppression of miR-520f-3p effectively offsets the effects of melatonin on the growth and metastasis of chondrosarcoma. Therefore, our research suggests that melatonin has therapeutic potential for reducing the carcinogenesis and metastatic potential of chondrosarcoma through the miR-520f-3p/MMP7 axis (Nguyen et al., 2023). Melatonin's anticancer efficaciousness, utilizing information from clinical, laboratory, and epidemiological studies; special attention was given to the mechanisms of action. (Ya Li and others, 2017). Some of the underlying processes include antioxidant action, modulation of melatonin receptors (MT1 and MT2), promotion of apoptosis, regulation of pro-survival signaling and tumor metabolism, inhibition of angiogenesis and metastasis, and induction of epigenetic modification. Unlike its powerful antioxidant action in healthy cells, it may create oxidative stress in cancer cells, which would add to its oncostatic effects.(Reiter and others, 2023) The protective effect of melatonin against doxorubicin-induced cardiotoxicity. Studies have shown that in mitochondria damaged by doxorubicin, melatonin can prevent the depolarization of the mitochondrial membrane, restart ATP synthesis, and maintain mitochondrial biogenesis. By promoting mitochondrial fragmentation, which in turn reduced mitochondrial activity, melatonin lessened the deleterious effects of doxorubicin (Attachaipanich et al.,2023). Melatonin, when used alone or in combination, seems to be a promising treatment for early-stage breast cancer because of

its history of minimal toxicity over a wide dose range. Kubatka and colleagues, 2018). The immunohistochemical investigation demonstrated the antiproliferative effects of melatonin and ascorbyl palmitate by a decrease in Ki-67 expression. Our melatonin and ascorbyl palmitate combination inhibited the invasion and metastasis of cancer cells by reducing the protein expression of MMP-9 (El-Far et al., 2023).

MELATONIN AND SKELETAL DEVELOPMENT

Research has indicated a connection between bone metabolism and melatonin. Within the constraints of this animal experiment, our results showed that melatonin gel has potential use as a bone-formation stimulator. The results of this study indicate that ossification percentages in the melatonin groups are higher than in the control group in a dose-dependent way. This is because ossification is more affected by 5% melatonin gel.(Golpasandhagh et al.,2023) its anti-inflammatory properties and possible role in the development of peri-implant bone.(Najafi and Salomó-Coll 2017 and 2018)There have been reports of melatonin's beneficial effects on bone repair around titanium dental implants. Because of its anti-inflammatory, antioxidant, bone cell-regulating, and collagen-synthesizing qualities, melatonin may be essential for all stages of bone regeneration. Research indicates that administering melatonin topically at the site of osteotomy during implant implantation can promote increased bone-to-implant contact, as well as increased bone mass and density surrounding dental implants, especially during the initial phases of healing (López-Valverde et al., 2021) Furthermore, by blocking the nuclear factor kappa B (NF-kB) signaling pathway and lowering RANKL protein levels, melatonin can prevent peri-implantitis (Wu et al.,2021). A melatonin-infused hydrogel template allowed for whole periodontal regeneration by speeding up bone growth and improving its quality. Additionally, the scaffold avoided epithelial cell entrapment and expansion in furcation defects (Abdelrasou et al., 2022)

FUTURE SCOPES

Researchers are studying the physiological effects and antioxidant properties of melatonin to better understand its role in normal and abnormal neurodevelopment. A major issue when considering wet or dry pet food formulations is ensuring that components are robust against industrial pet food processes like extrusion, sterilization, etc. There has been extensive in vitro and in vivo scientific research conducted to determine how well the formulations work. We describe new methods for nanoencapsulation as a means of enhancing stability and functionality. It is crucial to discover a biomolecule that could counteract the manifestations of diabetes and its associated complications, as the current modalities are unable to fully control them. These manifestations include insulin resistance, β-cell loss and dysfunction, oxidative stress, inflammation, and other diabetes-related problems.

The study should take into account the addition of more species and cardiac ischemia/reperfusion models. The results of these investigations will advance knowledge on the potential importance of melatonin use in oxidative heart damage cases involving humans.

In conclusion, research on animals has demonstrated how melatonin affects endocrine pathways, growth and development, immunological response, and cardiovascular health. Antioxidant capacity variations impact the physiological changes brought forth by melatonin. Modifying endogenous melatonin release and tampering with photoperiod in cattle can have major effects on growth, immune system function, cardiovascular health, and core body temperature—all of which are critical components of the animal agriculture industry. Past research has focused on connecting melatonin to the control of

reproductive performance in livestock species; however, this study has shown new mechanisms that need to be considered when considering animal agriculture.

CONCLUSION

Melatonin's characteristics have been shown to affect endocrine pathways, growth and development, immunological response, and the cardiovascular system in all species. Melatonin contributes to melatonin-mediated physiological changes via modifying antioxidant capacity. In livestock, alterations to endogenous melatonin release and photoperiod disruption have a significant impact on reproduction. This summarizes the therapeutic potency in the management and prophylaxis of diabetes and obesity. Implicate melatonin in controlling several cattle animals' reproductive processes. This study outlines melatonin's therapeutic potential in a variety of diabetes models and addresses concerns about whether or not it is a safe medication to treat diabetic consequences and symptoms, such as inflammation, oxidative stress, ER stress, mitochondrial dysfunction, metabolic dysregulation, and so forth. There are several proposed mechanisms explaining melatonin's biological effects. Melatonin not only appears to regulate development on its own, but when taken in adjuvant circumstances, it may also improve chemotherapy's efficacy and lessen its adverse effects. Its effectiveness, large safety margin, and absence of significant toxicity over a broad dose range have all contributed to its underutilized anti-cancer potential.

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How to cite this article: Jumnake AR, Patodkar VR, Gavali NE, Sardar VM. and Mehere PV. Advances in Melatonin Research – A Review. *Chron Aquat Sci*. 2024;1(10):152-174