Review Article
ISSN (Print): 0971-913X
J Endocrinol Reprod. *Vol 27(2), 73-90, June 2023, DOI: 10.18311/jer/2023/33014* *ISSN (Online): 2455-1244*

A Crosstalk Between Pineal and Major Extra-Pineal Sources of Melatonin and its Role in Ovarian Growth and Maturation in Fish

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Abstract

Pinealocytes of the pineal gland in vertebrates mainly synthesize melatonin (5-methoxy-*N*-acetyl-tryptamine). Moreover, melatonin is synthesized in several extra-pineal cells, including the photoreceptor cells of the retina, the cells of the gut, and the hepatocytes of the liver in different vertebrates, including fish species. One of the remarkable features of pineal and retinal melatonin is that it is produced rhythmically in synchronization with the environmental Light-Dark (LD) cycle, with a daily nighttime peak. However, the melatonin synthesis in tissue/cells from the extra-pineal and extra-retinal origin(s) may not always undergo photoperiod-regulated daily variations but is also dependent on the environmental food entrainment factors (in the gut), acting as the most reliable synchronizer(s) in its daily rhythm features. Moreover, the regulation of the liver and ovary (important for fish reproduction) is unclear. In this review, we attempt a comparative account of the nature and regulation of endogenous melatonin synthesis between a source like the pineal gland and many other non-pineal origins, which have gained serious attention in the last ten years. We also review the functions of melatonin in regulating fish ovarian growth and maturation. The physiological melatonin levels, manipulated either endogenously (by photoperiodic modulations) or exogenously (by injections or by feeds), have tremendous effects on reproductive events in fish at the age of its first maturity, as revealed in recent findings. Characterization and identification of the importance of pineal gland melatonin in the growth of the oocytes via the hypothalamic-pituitary-gonadal axis have been explored several years back. The identification of melatonin receptors about fourteen years back on the wall of developing oocyte spurt the breakthrough, which introduced the concept of direct control of melatonin on developing oocytes. Thus, this review gains uniqueness by addressing the latest developments recorded in the field of melatonin and fish reproduction, particularly in improving oocyte maturation. Nonetheless, an attempt has been made to underline approaches that need to be developed to apply the molecule in large-scale aquaculture.

Keywords: Extra-Pineal Sources, Fish Oocyte Growth and Maturation, Fish Reproduction, Melatonin, Pineal Organ

1. Introduction

Melatonin (5-methoxy-*N*-acetyl-tryptamine) of teleost, principally synthesized from the pineal organ, is known to play a critical role in the direct perception of light from the environment concomitant with diurnal as well as seasonal photoperiodic changes in the regulation of diverse physiological functions[1,2] including reproduction[3,4]. The chronobiological rhythm of this wonder molecule is conveyed by converting the changing environmental signals, which are ultimately transcribed into an endocrine signal[5] that informs the body's internal physiology about the time and the month of the calendar year of a season. In recent times, researchers found a strong link between the role of melatonin in reproduction[6,7] not only in different mammals but also in lower groups of vertebrates such as fish[3,4]. The varying length of the nighttime melatonin transmits the signal by coordinating three different sites of action: (i) hypothalamus, (ii) pituitary, and (iii) gonads[8]

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Article Received: 10.03.2023 Revised on: 08.07.2023 Accepted on: 16.07.2023

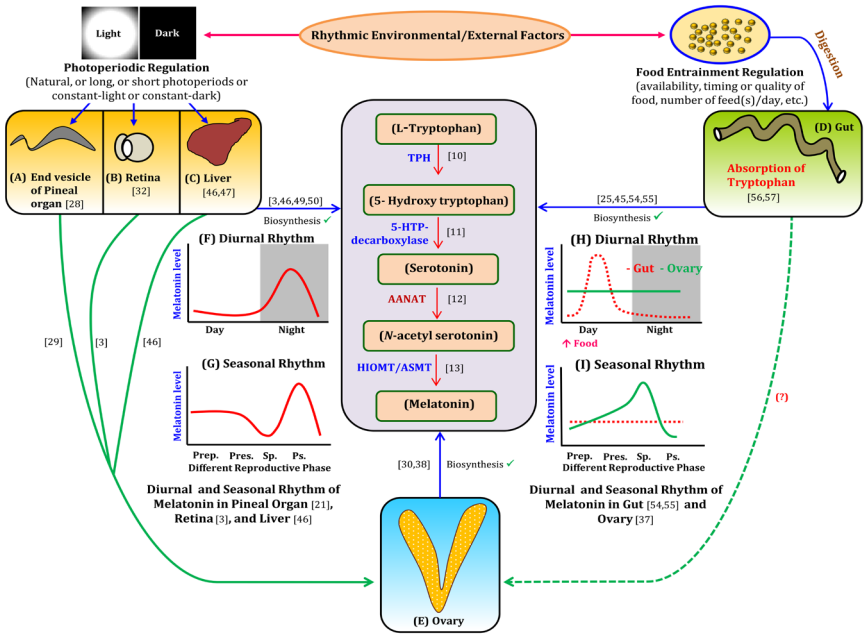

Figure 1. Diagrammatic representation of melatonin biosynthetic pathway within **(A)** the end vesicle of pineal organ, **(B)** retina, **(C)** liver, **(D)** gut, and **(E)** ovary in fish. Melatonin synthesis in the pineal organ, retina, and liver is under the control of environmental Light-Dark (LD) conditions such as natural (NP; LD 12:12 h) or long (LP; LD 16:08 h), or short (SP; LD 08:16 h) photoperiods or constant-light (LL; LD 24:00 h) or constant-dark (DD; LD 00:24 h), while in the gut tissues melatonin synthesis is influenced by rhythmic environmental/external features like food entrainment factors, viz., availability of food, timing of food supply, number of feeds per day, quality of food, etc. In the inset, rhythm characteristics of **(F)** diurnal and **(G)** seasonal profiles in LD-entrained melatonin-producing tissue (pineal, retinal, and liver) are shown on the left. On the right, the **(H)** diurnal and **(I)** seasonal rhythm of the gut (red dotted line) and ovarian melatonin (green solid line) are shown. As per the summary of information gathered, pineal, retinal, liver, and ovary melatonin exhibit an influential role in ovarian functions, while, to date, no such data are available on the impact of gut melatonin on fish reproduction. Prep. = preparatory; Pres. = pre-spawning; Sp. = spawning; Ps. = post-spawning.

via the Hypothalamic-Pituitary-Gonadal (HPG) axis about the time of an annual cycle[9], and the testicular and ovarian development is regulated based on this changing melatonin secretion by the pineal organ in fish.

1.1 Pathway of Melatonin Biosynthesis

Melatonin is synthesized in four sequential steps from L-tryptophan (one of the crucial amino acids) within the melatonin-synthesizing tissue (Figure 1). L-tryptophan is first transformed to 5-Hydroxy-Tryptophan (5-HTP) by Trp-5-Mono-Hydroxylase (TPH)[10] within the mitochondria. In the second step, the 5-Hydroxy-Tryptamine (5-HT/serotonin) is synthesized from 5-HTP following decarboxylation by aromatic amino acid decarboxylase, which occurs in the cytosol[11]. In the third step, 5-HT is acetylated into *N*-acetyl serotonin by the rate-limiting enzyme Arylalkylamine-*N*-Acetyltransferase (AANAT)[12]. In the fourth or final step, *N*-acetylserotonin is *O*-methylated by *N*-Acetylserotonin *O*-Methyltransferase (ASMT), previously known as Hydroxyindole-*O*-Methyltransferase (HIOMT), to produce melatonin[13]. Notably, three TPH (TPH1a, TPH1b, and TPH2)[14], two AANAT [AANAT1 (AANAT1a and/or AANAT1b) and AANAT2][15], and two ASMT[16] isoforms have been identified in the teleost, which plays an essential regulatory function in the synthesis of melatonin. Two TPH isoforms are known to exist in most mammals[17,18]; TPH1 is only found in the pineal organ and peripheral tissues, whereas TPH2 is localized in the brainstem raphe nuclei[19]. Furthermore, tissue-specific expression of TPH has been reported in zebrafish wherein TPH1 (a and b) is

primarily involved in photoreception, phototransduction, and melatonin production[20]. The unique feature of teleost AANAT among vertebrates is having two subfamilies[21,22]. In addition, an earlier study[15] found that AANAT1 is primarily responsible for mediating the metabolism of serotonin and dopamine, as well as melatonin production in the retina, whereas AANAT2 is more specific for the production of melatonin in the fish pineal. Further, two ASMT subfamilies have evolved due to whole-genome duplication close to the origin of teleosts[23,24] and subsequent mutations in the duplicated genes. It has been noted that the higher expression of the AANAT gene in a melatonin synthesizing tissue is usually associated with higher expression of the ASMT gene and ultimately to the elevation of the final product melatonin[25]. In contrast, according to a recent report[26], the activity of the ASMT, the final enzyme for synthesizing melatonin from *N*-acetylserotonin, also seems to be a vital step during the biosynthesis of melatonin.

1.2 Pineal and Extra-Pineal Sources of Melatonin

The pineal gland is located at the roof of the diencephalon or third ventricle of the brain, which performs the function of an endocrine gland in a higher group of vertebrates and secrete LD-regulated melatonin. But in this case, the pineal gland does not retain any photoreceptive property; instead, the retina perceives the photic information. However, the mechanism of photo-perception is different in vertebrates like fish, amphibians, and reptiles. Here, the pineal is a photoreceptive structure in addition to endocrine function (glandular functions) and is named the 'pineal organ'[27]. A complex of three distinct structures represents the pineal organ in teleost fish: an anterolaterally extended, dorso-ventrally compressed vesicular body - the end vesicle situated close to the cranium, linked to the brain by a very long pineal stalk, which at the cerebral end is encircled by highly folded plexiform saccular - dorsal sac[28]. However, an immunocytochemical study confirmed the presence of melatonin-secretory pinealocytes only in the end vesicle portion of the pineal complex of fish[29]. Therefore, melatonin biosynthesis was investigated in several studies using the end vesicle as the primary target[30,31].

Subsequent studies over the last fifty years detected melatonin in various extra-pineal tissues and cells in animals, including the photoreceptor cells of the retina[3,32], the acinar cells of the Harderian gland[33], the enterochromaffin cells of the gut[34] and the hepatic cells of the liver[35]. Studies have shown the presence of all the vital photoperiodic-driven melatonin biosynthesizing enzyme genes (TPH1, AANAT1, AANAT2, and ASMT) in the retina in addition to the pineal gland in the tropical carp[30,31]. Though day-night variations were noted in both tissues, the pineal and retina may show different patterns of biosynthesizing gene expression in the seasonal cycle[31]. It was also pointed out that the rhythm parameters of various melatonin biosynthesizing enzyme genes in these two organs vary and/or shift differently. Additionally, under the influence of different photoperiodic conditions, the pattern of mRNA expression of the melatonin biosynthesizing enzyme genes in the retina and pineal organ changes[36]. This investigation reveals a distinctive way of mRNA transcripts for the genes TPH1, AANAT1, AANAT2, and ASMT in the retinal and pineal organ; the pineal melatonin biosynthesizing enzyme genes exhibited a pattern similar to that of serum levels of melatonin, and the retinal genes underwent a dramatic change with photoperiod.

Recent reports have confirmed the existence of melatonin in the follicular cells of the ovary; however, the synthesis of this molecule within the ovary has not been evident, as the existence of AANAT, the critical enzyme for melatonin biosynthesis, has not been noted in the ovarian tissue[37]. In contrast, another study demonstrates the mRNA of all the melatonin biosynthesizing enzyme genes in the zebrafish ovary (*Danio rerio*) under varied photoperiodic conditions. Moreover, this study also confirmed the capability of the zebrafish ovary in the biosynthesis of melatonin by estimating AANAT2 under both *in vivo* and *in vitro* states with a significant daily variation by qRT-PCR analysis in the ovary[38].

Surprisingly, the regulation of melatonin synthesis in extra-pineal tissues, such as the gut, differs from the pineal organ[39]. The high expression levels of melatonin-synthesizing enzymes have indicated endogenous synthesis of melatonin in the gut[40,41]. The study in goldfish showed mRNA expression of gAANAT2 in both the anterior gut and hindgut[16], which is further supported by a study[42] that found a rhythmic AANAT activity in the anterior gut of the same fish. Munoz-Perez *et al.*,[43] have shown a significant alteration in melatonin levels and the mRNA expression of AANAT1, AANAT2, and ASMT

in the mucosa and the gut wall of trout. A recent study[25] also demonstrated that the AANAT2 and ASMT genes are vividly expressed in the digestive tract. The greater expression of the AANAT2 gene, rather than AANAT1, indicates the significance of the AANAT2 isoform in melatonin production in carp. Moreover, melatonin biosynthesizing enzyme genes in the zebrafish digestive tract and their daily mRNA expression profile have been investigated under different feeding conditions involving regular photoperiods[44]. This study demonstrated that an alteration in the feeding cycle could alter the melatonin synthesizing system because the acrophase of the TPH1, AANAT2, and ASMT transcripts in the altered feeding was the reverse of that in the regular feeding. Moreover, the fish gut has shown higher melatonin synthesis in association with AANAT protein expression, the rate-limiting enzyme of the melatonin biosynthetic pathway[1], concomitant with the feeding-fasting cycle[45], indicating endogenous synthesis of melatonin by gut tissue. Similar expression of the AANAT protein and the hormone melatonin was also detected in the hepatic tissues, and it was discussed in favour of local synthesis of hepatic melatonin[46]. Further, hepatic melatonin exhibited an altered circadian rhythm, and, unlike pineal or serum melatonin, the peak of hepatic melatonin titer was recorded at the early dark phase during the four reproductive stages of a yearly cycle. The hepatic melatonin exhibited the highest value in the post-spawning phase and the lowest in the spawning phase[47] (Figure 1).

1.3 External Regulators of Melatonin Rhythm in the Pineal Organ and the Extra-Pineal Origins

One of the remarkable features of melatonin, measured in the tissue extracts of the pineal gland/organ in all the animals studied, including fish, is that it undergoes rhythmic variations in a daily cycle in synchronization with the environmental LD cycle with a peak at midnight[21,48] (Figure 1). This pattern of rhythmicity is partially due to a dark-dependent rise in the activity of Arylalkylamine-*N*-Acetyltransferase (AANAT), which catalyzes the transformation of serotonin to *N*-acetylserotonin[1]. Notably, three variants of night-time melatonin rhythm (namely type - A, -B, and -C) have been identified[21] in different vertebrate groups, including fish. The A-type profiles are characterized by a discrete peak in the late dark phase, e.g., Atlantic cod *(Gadus morhua)* and Haddock *(Melanogrammus aeglefinus)*. In contrast, B-type rhythms are described by a distinct peak in the mid-dark phase, e.g., Nile tilapia *(Oreochromis niloticus niloticus)*, and C-type rhythms exhibit a rapid increase in melatonin nearly after the start of darkness, e.g., rainbow trout *(Oncorhynchus mykiss)*, Atlantic salmon *(Salmo salar)*, Atlantic halibut *(Hippoglossus hippoglossus)* and most teleosts[21]. However, the investigation on carp (*Catla catla*) discovered for the first time that the nature of the nighttime peak of pineal[49] and serum melatonin[29] in the same species might change from A-type (during the preparatory phase) to B-type (during the remaining parts of a reproductive cycle) in different stages of an annual process. This indicates the diverse nature of melatonin sensitivity in gonads subjected to the reproductive status of the fish.

Melatonin immuno-reactive cells have been confined in the Outer Nuclear Layer (ONL), Outer Plexiform Layer (OPL), and Inner Nuclear Layer (INL) of the retina. Two cell types are involved in melatonin biosynthesis; Müller and photoreceptor cells. Immuno-fluorescence study indicates that perikarya of the ONL, the synaptic processes of photoreceptor cells of the OPL, contain high intensities of melatonin[50]. In most of the animals studied, the striking feature of retinal melatonin, like pineal, is that it is synthesized rhythmically with a sharp day-night variation in synchronization with the external LD cycle[2]. The melatonin level in the retina is high during scotophase and low during photophase[3,50]. It is argued that melatonin, which originates from the retina, might function as a modulator of neurotransmission and neuronal excitability of this tissue[51]. Retinal melatonin may have autocrine, paracrine, or neuroendocrine actions[52].

In contrast to the melatonin profiles noted in the pineal organ and retina, melatonin synthesis and secretion by an extra-pineal and extra-retinal source like the gut do not come under environmental photic control[53–55]. Remarkably, in fish, the chronological features of the gut melatonin were found to fluctuate with the environmental food entrainment factors such as availability of food, the timing of food supply, number(s) of feed per day[45], quality of food[56,57], which act as the most reliable synchronizer(s) in daily rhythm features of gut melatonin[58] (Figure 1). The melatonin levels in the gut showed a different rhythmic pattern on the availability of foods, quality of food, and

most notably on, the feeding time. When fish was fed daily at different time points, an intense impact of feeding time on the gut melatonin was found.

Irrespective of environmental light and temperature variations experienced by carp in their natural habitat, ovarian melatonin content did not show significant day-night variations. On the contrary, ovarian melatonin concentration showed substantial annual fluctuations, with a peak during spawning and a lowest during post-spawning[37]. The ovarian melatonin concentration during spawning was approximately five times greater than noted during the post-spawning phase promoting the knowledge of a probable role of the endocrine signal in the ovary. On the other hand, a recent study[46] on carp (*Catla catla*) reported the rhythm features of melatonin in both the serum and liver under natural photo-thermal conditions. The day-night melatonin levels in the hepatic tissue portrayed an indistinguishable pattern of differences, irrespective of reproductive seasons, with a peak at the onset of night and a lowest at midday. The expression of AANAT protein, like melatonin titers, in the liver showed maximum levels in the post-spawning phase and minimum in the spawning season.

2. Environmental Regulation of Oocyte Growth and Maturation

The growth and development of the ovary in most teleost are discontinuous and marked by some specific characteristics in seasonally breeding fish. Breeding in fish shows its peak activity in a short period, headed by an extended and complex preparation procedure. The breeding time of each species is so precisely scheduled that offspring is created in optimum environmental conditions to ensure maximum survival. Generally, temperate zone fish spawn during spring and early summer, while others spawn during autumn. Freshwater fish from the Murray-Darling River System of New South Wales, Australia, spawn when flooded waters come into contact with dry soil[59]. Similarly, the fish in the central Amazonian floodplain lakes used to spawn during the rainy season[60]. In the Indian subcontinent, most freshwater teleosts breed during the monsoon when rainfall is the heaviest.

In the subtropical and tropical regions, the peak spawning period of the fish is associated with monsoon[61], which is related to the synchronization of spawning. It has been suggested to play an influential role in stimulating the release of gonadotropins (FSH, LH), which finally leads to spermiation or ovulation[62]. However, the prime candidates among all different environmental components that are responsible for the complicated preparation (development) of the ovary (or rather gonad) for the rhythmic activity of reproductive events in fish are light and temperature. Synchronization of physiological and environmental events is one of the most potent roles of the fish neuroendocrine system, comprising sensors and circadian oscillators like the pineal organ, the lateral eyes, and the hypothalamic suprachiasmatic nuclei. This circadian oscillator system in teleost is located in the pineal organ and the eyes, among which the pineal organ is considered the most critical component of the endocrine system, which conveys the message of changing photic environment and has a conserved role in the cyclical synthesis and release of melatonin to influence the seasonality of ovarian activities[63].

2.1 Seasonal Ovarian Cycle in the Subtropical Teleosts

Catfish of subtropical regions are seasonal breeders and display an annual gonadal cycle in which two consecutive physiological events occur. The first set of events leads to gradual enlargement of the ovary with concomitant vitellogenesis before spawning[64]. The second set of events involves ovulation and spawning during the monsoon season (July to August), the prime time for breeding. A similar trend is noticed in carp, though the breeding periodicity of carp varies with the geographical distribution of species. In Israel, the carp typically breed in April and May[65]. In France, the common carp spawns in the summer[66]. Indian major carp *Catla catla*, which represents the only non-air-breathing fish in India that has been considered for extensive experimental studies to understand the mechanism of environmental and endocrine control of seasonal reproduction, is known to breed during the monsoon[67,68]. Based on the investigation made on the ovary, the seasonal breeding cycle of these subtropical fish has been categorized into four phases: (a) preparatory (January–March), (b) pre-spawning (April–June), (c) spawning (July–August), and (d) post-spawning (September-December) phase, each of which displays some definite standard features. In the

first event, during the preparatory and pre-spawning phases, the ovary undergoes enlargement by forming yolky oocytes through the process of vitellogenesis. In the second event, maturation, ovulation, and finally, the release of oocytes occurs through spawning. After spawning, the ovary remains in the gametogenically inactive stage with abundant degenerated/atretic follicles (non-spawned eggs) and postovulatory follicles. The steroidogenic cascades and vitellogenesis cannot be triggered during this phase. This phase is the previtellogenic or post-spawning phase (September-December)[29,68].

2.1.1 Vitellogenic Phase or Growth Phase and Post-Vitellogenic Phase or Maturation Phase of Oocyte

During vitellogenesis, the yolk precursor protein vitellogenin is synthesized in the liver under stimulation of 17β-estradiol (E2) and transported to the ovary via circulation, where the growing oocytes (Stage I) take it up. E2 is synthesized and secreted from the granulosa cells of the ovarian follicles and acts on the liver during the process of vitellogenesis[69] (Figure 2). Before ovulation, the ovary occupies almost the entire body cavity with large round yolky oocytes (Stage III), which remain arrested in the late G2 of the first meiotic prophase and wait for final maturation, which is also hormonally controlled. The process involves Germinal Vesicle Breakdown (GVBD), chromosome condensation, the first meiotic spindle assembly, and the first polar body extrusion. In most teleosts, 17α, 20β-dihydroxy-4-pregnen-3-one (17α, 20β-DHP) serves as a potent Maturation-Inducing Hormone (MIH)[70], which acts on oocyte membrane receptors and activates the Maturation-Promoting Factor (MPF) in the oocyte cytoplasm to initiate final maturation[71]. MPF is composed of two subunits: (a) cyclin B, a regulatory subunit, and (b) cyclin-dependent kinase (Cdk1, or Cdc2, or p34 kinase), the catalytic subunit[72]. Under the stimulus of MPF, oocytes experience severe morphological modifications associated with advancing the meiotic cell cycle. In this process, the oocyte nuclear envelope or Germinal Vesicle Breakdown (GVBD) occurs at the prophase/metaphase transition, which is generally considered a symbol of oocyte maturation[73] (Figure 2).

3. Melatonin and Hypothalamic-Pituitary-Gonadal Axis

Available data on the structures and functions of the piscine endocrine system and its role in reproduction is based on the studies of species inhabiting mainly the temperate zone where seasonal fluctuations in daily photoperiods are more prominent. The individual function of the pineal organ[28] and its hormone melatonin[29] and photoperiods[67,74,75] in reproduction has also been studied in sub-tropical carp. The pineal hormone melatonin transmits diurnal and seasonal time of the day information to many tissues and is crucial in regulating reproduction in seasonally breeding vertebrates[76]. As melatonin is rhythmically synthesized by the pinealocytes[49] and retinal photoreceptor cells[50], with a peak during the dark phase, it can interact with several peripheral and central tissues, including the brain[77], pituitary[78] and also gonads[79,80] in different vertebrates, including fish. The study on European sea bass (*Dicentrarchus labrax*) indicates that melatonin plays a neuromodulatory role in the brain via G-protein-coupled melatonin receptors[63]. The existence of melatonin receptors in the hypothalamus and pituitary suggests the role of melatonin in reproduction via the HPG axis[81] (Figure 2). Recent work on zebrafish suggested the involvement of melatonin in regulating GnIH and GnRH functioning, thereby influencing the development and maturation of ovary[82].

3.1 Effects of Altered Photoperiods and Exogenous Melatonin

Considering melatonin as the physiological messenger of the duration of darkness and, thereby, light, extensive studies have aimed at the role of endogenous and/or exogenous melatonin on carp ovarian growth and maturation[29,67,83]. The physiological role of melatonin in regulating the reproductive events in adult female carp was studied by manipulating the environmental photoperiods (endogenous melatonin)[74,75] as well as by administration of exogenous melatonin (through intramuscular injection) during different phases of reproduction in the carp[29]. Experimental studies provided evidence that exposure of carp to long photoperiods (LP; LD 16:08 h) (which reduces the physiological level of melatonin) during the pre-spawning phase leads to

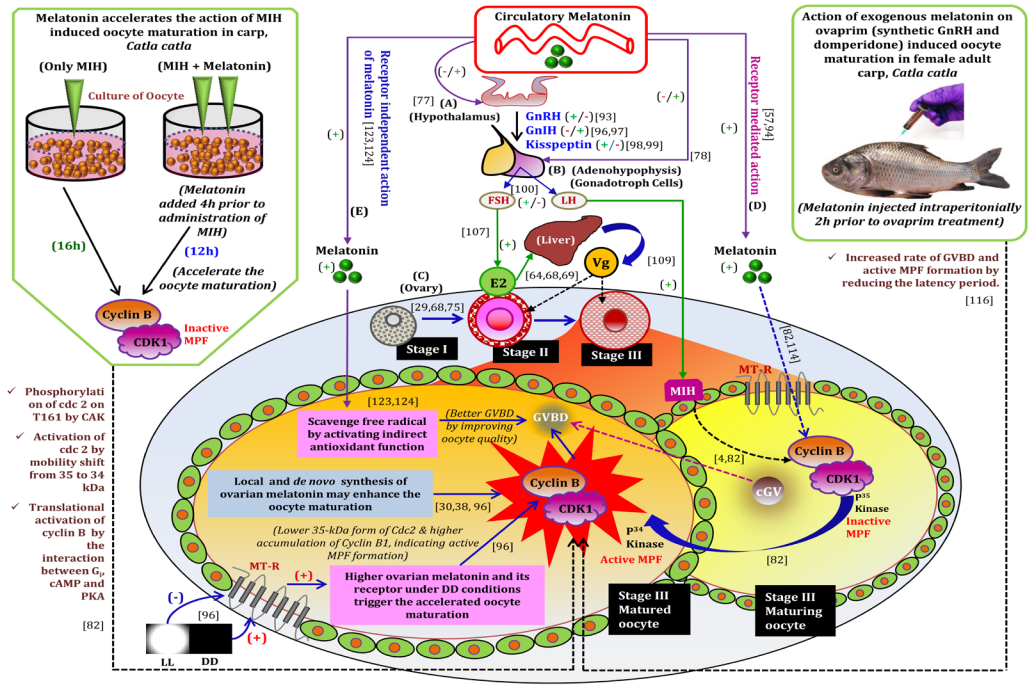

Figure 2. Schematic presentation of the summary of information gathered from different studies to explain the possible role of melatonin in oocyte growth and maturation. Primarily, melatonin acts on the hypothalamus **(A)**, pituitary **(B)**, and ovary (gonad) **(C)**, the three components of the HPG axis. In addition, it can also exhibit its action directly via oocyte receptors **(D)** or independent of the receptor **(E)**. Once available in circulation, melatonin act on the hypothalamic secretion of GnRH, GnIH, and Kisspeptin to control the secretion of the gonadotroph cells of the adenohypophysis. Further, direct control of melatonin in the pituitary is evidenced from literature to control the secretion of FSH and LH from gonadotroph cells. FSH acts on the granulosa cells of the ovarian follicle to regulate the synthesis of 17β-estradiol (E2), which causes the synthesis of vitellogenin protein (Vg) in the liver. Vg, through circulation, is deposited in the developing oocyte; as a result, the Stage I oocyte is transformed into Stage II and then into Stage III within the ovary. The receptor-mediated direct action of melatonin has been demonstrated in the Stage III oocyte (right side enlarged view of maturing Stage III oocyte) of carp. Melatonin interacts with its receptor (MT-R) in the oocyte membrane to regulate the LH-induced Maturation-Inducing Hormone (MIH) and to accelerate its action for the formation of active MPF (a complex of cyclin B and Cdk1) from its inactive state. This induces GVBD in stage III matured oocytes (Left side magnified view of Stage III matured oocyte). In the upper left side inset, the experimental evidence of an *in vitro* study on the carp *Catla catla* (D) is shown. It shows that melatonin accelerates the action of MIH-induced oocyte maturation. The receptor-independent direct action of melatonin can lead to a better rate of maturation or GVBD by forming better-quality oocytes. In the lower left side inset, experimental evidence of both DD and LL and the role of ovarian melatonin has been shown. Under the influence of DD, higher melatonin levels through ovarian melatonin receptors accelerate the GVBD. It also reveals the role of locally synthesized ovarian melatonin to induce oocyte maturation. In the upper right side inset, the action of exogenous melatonin on ovaprim (synthetic GnRH and domperidone) induced oocyte maturation in female adult carp, *Catla catla*, has been shown by injecting melatonin 2h before ovaprim dose. This leads to an increased rate of GVBD and active MPF formation by reducing the latency period. GnRH = gonadotropin-releasing hormone; GnIH = gonadotropin inhibitory hormone; FSH = follicular stimulating hormone; LH = luteinizing hormone; E2 = 17β-Estradiol; Vg = vitellogenin; MIH = maturation inducing hormone; CDK1 = cyclin-dependent kinase 1; MPF = maturation promoting factor; cGV = central germinal vesicle; GVBD = germinal vesicle breakdown; MT-R = melatonin receptors; DD = continuous dark; LL = continuous light.

precocious maturation of the ovary[75]. Notably, during the preparatory phase, an increase in the vitellogenin level and the activity of steroidogenic enzymes was recorded. However, no ovarian weight gain and a relative number of different oocyte stages were found when the fish were exposed to LP during the preparatory phase. Similarly, no ovarian response was found when the fish were transferred to LP during the spawning and the post-spawning stages. However, the short photoperiod (SP; LD 08:16 h) (which increases the physiological availability of melatonin) was found to have an inhibitory effect on ovarian growth and maturation during pre-spawning and spawning phases or have no impact on ovarian functions during preparatory and post-spawning phases of an annual cycle[75].

On the other hand, exogenous injection of melatonin for 15/30 days in carp also accelerated oocyte growth during the preparatory phase, but a reduction in the number of developing oocytes (Stages II and III) was noted during the pre-spawning and spawning phases. Interestingly, no ovarian response to exogenous melatonin was found during the post-spawning phase[29]. Thus, the administration of exogenous melatonin exhibits a pro-gonadal effect during the preparatory phase but an anti-gonadal response during the pre-spawning and spawning phases of carp (*Catla catla*)[84] as well as catfish (*Heteropneustes fossilis*)[85]. Moreover, treatment with exogenous melatonin by oral route with melatonin-rich pellets may cause a decrease in spawning frequency, number of spawned eggs, Gonado-Somatic Index (GSI) in females, and decreased sperm count, spermatocrit, and spermatozoa activity index in male Nile tilapia (*Oreochromis niloticus*)[85]. Similarly, another recent study in freshwater catfish (*Mystus cavasius*) revealed that administration of melatonin by the same oral route could reduce the level of GSI, the number of vitellogenic oocytes in the ovaries, and can repress serotonergic activity during the spawning season[87]. This indicates that, like exogenous melatonin treatment by injection, the application of melatonin with fish feed also has an inhibitory effect on gonadal maturity during the spawning phase. However, further investigations are essential to understand the role of melatonin on pubertal onset and gonadal maturation.

3.2 Influence of Melatonin on the Reproductive Endocrine Axis

There is much experimental evidence that melatonin acts through the HPG axis[79,88] or with brain and peripheral regions such as the diencephalon (hypothalamic portion)[77], pituitary[78], ovary[4], and liver (site of vitellogenesis)[89]. Thereby, the hypothalamus (gonadotropin-releasing hormone, or GnRH), pituitary (follicle stimulating hormone, or FSH; luteinizing hormone, or LH), and ovary (E2) levels are influenced by melatonin to control the reproductive axis in fish[90] (Figure 2).

3.2.1 Regulatory Effects of Melatonin on the Hypothalamus

In several fish species, melatonin showed an inverse relationship with the GnRH, a decapeptide hormone from hypothalamic neurosecretory cells that acts on its receptors in the pituitary to regulate the production and release of gonadotropins from the adenohypophysis[91]. It is also claimed that melatonin has neither anti-gonadotrophic nor pro-gonadotrophic effects. Instead, the changing duration of the night leads to changing secretory patterns of melatonin, which provides the idea about the time of the years by conveying the message over the HPG axis[9,21]. According to Malpaux *et al.*,[92] and Revel *et al.*,[93] melatonin does not seem to act on GnRH neurons, while others stated that melatonin might act directly on GnRH neurons under the influence of PKA, PKC, and MAPK pathways[94]. The exact mechanism of melatonin action in the brain must be investigated further in various fish species.

The identification of Gonadotropin-Inhibitory Hormone (GnIH), a newly discovered hypothalamic neuropeptide that, unlike GnRH, actively inhibited gonadotropin release in quail[95] and other vertebrates, including teleosts[96], has added a new dimension to the current understanding of the hypothalamic regulation of pituitary-gonadal functions in vertebrates (Figure 2). Melatonin appears to induce GnIH expression by regulating directly the GnIH neurons via the melatonin receptor. Transcription of the GnIH gene in the brain of zebrafish (*Danio rerio*) upregulated in a constant lighting environment when melatonin was recorded low in the whole brain and ovary but downregulated in continuous dark conditions when melatonin was recorded high in the mentioned organs. Similarly, reports show that exogenous melatonin treatment can reduce GnIH gene expression in a dose-dependent manner in the cultured brain[82]. Moreover, in Nile tilapia (*Oreochromis niloticus*), melatonin can suppress the HPG axis via the action of GnIH[97]. Thus, GnIH can influence the reproductive axis

by transducing photoperiodic information via changes in the melatonin signal[94]. However, further investigation into the role of GnIH and its interactions with GnRH and/or melatonin in determining reproductive periodicity in fish is needed.

Kisspeptin, the product of the kiss1 or kiss2 genes, has a stimulatory effect on GnRH neurons via its receptor (GPR54), causing the HPG axis to be upregulated. Kisspeptin and GPR54 are crucial players in the physiological regulation of reproductive maturation and function, including the timing of puberty. According to a recent study, oral administration of melatonin can reduce transcript levels of kisspeptin (kiss1 and kiss2), gonadotropin-releasing hormones (gnrh1), and the β-subunits of gonadotropins (fsh*β and* lh*β*) in the brain of the sapphire devil (*Chrysiptera cyanea*). Thus, it was demonstrated that long-term treatment with melatonin may impair the transcript levels of genes concerned with the HPG axis in reproduction[98]. The dynamic control of GnRH secretion by the hypothalamic neurons transmits the negative and positive feedback effects on sex steroids, thereby regulating fertility and synchronizing the reproductive events with the environmental (photoperiodic) cues[99]. Available evidence suggests a functional relationship between melatonin and various hypothalamic peptides (GnRH, GnIH, and kisspeptin) regulating seasonal reproduction (Figure 2). Yet, more experimental evidence from diverse fish species must be gathered to support the hypothesis.

3.2.2 *Regulatory Effects of Melatonin on the Pituitary Gland*

The first evidence of melatonin in the regulation of gonadotropins (FSH and LH) came from a study on the Atlantic Croaker (*Micropogonias undulatus*)[100], in which it was found that a low dose of melatonin upregulates the LH release by pituitary cells in culture[101] while *in vivo* administration of melatonin during the light phase caused significant elevations in plasma LH levels in fish with fully developed gonads. Further, opposite results are also available where melatonin reduces the expression of LHβ as well as FSHβ mRNA[98,102]. Moreover, reports are also available to the effect that melatonin administration can reduce the LH content but stimulate FSH secretion[103]. Thus, by investigating the pituitary actions of melatonin, it can be argued that melatonin might modulate neuroendocrine functions by targeting the pituitary gland as well, but such modulation may differ in different groups of animals. There is convergent evidence to the effect that melatonin receptors (MT1 and MT2 subtype) are present in pike and trout pituitary glands[104], indicating regulation of seasonal reproductive events via melatonin (Figure 2).

3.2.3 *Regulatory Effects of Melatonin on Ovarian Sex Steroids*

The HPG axis is primarily responsible for synthesizing sex steroids and ultimately exerts their effect on fish reproduction. In general, ovarian steroidogenesis depends on the interaction between theca and granulosa cells, which are involved in follicular development and maturation. However, in some fish, such as medaka, the granulosa cells of preovulatory follicles can produce various steroid hormones without the involvement of theca cells[105]. In most fish, FSH stimulates follicular E2-synthesis and incorporation of vitellogenin into oocytes, while LH stimulates steroidogenic activity for the synthesis of progestins (17α, 20β-dihydroxy-4-pregnen-3-one or 17α, 20β DP) or Maturation-Inducing Hormone (MIH), the latter playing a crucial role in oocyte maturation[106]. The endogenous titer of E2 in carp maintains a high level during the spawning phase (June-August) as evidenced by the activity of ovarian steroidogenic enzymes such as 3-Hydroxysteroid Dehydrogenase (3β-HSD) and 17-Hydroxysteroid Dehydrogenase (17β-HSD)[107]. However, melatonin levels were highest during the post-spawning phase of an annual cycle (September-December)[29]. Irrespective of the reproductive stage, E2 levels in serum had a daily peak in the mid of the day and a lowest in the early morning, but in a seasonal cycle, E2 was found to be highest during the spawning phase. The serum MIH, on the other hand, failed to exhibit any significant daily variations and changed significantly over an annual cycle, with a shallow value in the preparatory phase (January-March), a gradual increase in the pre-spawning phase (April-May), a peak in the spawning phase, and was undetectable during the post-spawning phase[80]. Hong *et al.*,[108] investigated the potential effect of melatonin on the production of progestin, 17α, 20β DP, in mudskipper (spring spawn) with fully developed ovarian follicles during the spawning season and found that plasma levels significantly increased after melatonin injection. Numerous studies have established a role for

ovarian membrane progesterone receptor beta (mprb) in progesterone-induced oocyte maturation[106,109–111]. Notably, a recent study[82] showed that higher mprb expression in the oocyte under constant dark conditions indicates more oocyte maturation; in contrast, maturation in the oocyte was prohibited under constant lighting conditions. This reciprocal relationship could shed light on several reports that melatonin has a pro- or anti-gonadal effect in the same species at various times of the year[4,21]. Furthermore, melatonin uniquely counteracts the effects of estrogen by interacting with the estrogen receptor signalling pathway. Melatonin binds to its receptors and inhibits estrogen receptor expression, thereby preventing estradiol from attaching to its receptors[112]. Indeed, several views have been proposed to explain the anti-estrogenic action of melatonin in the reproductive system revealing that melatonin reduces estrogen production by modulating the various steroid hormone biosynthetic enzymes. This efficacy expounds the role of melatonin as a selective estrogen enzyme modulator[8,91,92] in a dose and time-dependent manner[113].

4. Melatonin in the Regulation of Oocyte Maturation

According to the available literature, it is presumed that an excess amount of melatonin, either added exogenously or produced endogenously, plays a significant role in regulating the annual ovarian activities in the carp. Still, the responsiveness of the ovary to the melatonin varied with the reproductive status of the fish[3]. In addition, it is generally believed that the action of melatonin on the ovary is mediated via the HPG axis[79,88]. But the demonstration of the melatonin receptor protein (MT1) (37 kDa) in the carp ovary[114] supported the hypothesis that melatonin exerts its action directly as well on the ovary, and modulates the activity of MIH[83] by altering membrane progesterone receptor (mpr) α and β expression[115] during maturation of oocyte following the formation of MPF. According to a recent report, melatonin pre-treatment in carp by intramuscular injection upgrades the ovaprim (synthetic GnRH and domperidone) actions on final oocyte maturation[116].

The pre-ovulatory gonadotropin surge promotes final oocyte maturation or the resumption of meiosis in vertebrates. In most fish, the oocyte maturation is mediated by the MIH that activates the cytoplasmic MPF by the oocyte membrane-induced signalling mechanism. The *in vitro* study by Chattoraj *et al.*,[83] reported that melatonin incubation with denuded oocytes, especially 4 h before the addition of MIH, stimulated the MPF functions. Melatonin pre-treated MIH incubated oocytes exhibited increasing cyclin B levels up to 12 h, which resulted in the early maturation of oocytes compared to MIH alone. Notably, only MIH-mediated oocyte maturation requires about 16 h of incubation. Moreover, the determination of H1 kinase activity as an indicator of MPF activity in oocytes reveals that melatonin pre-incubation increases MIH stimulation of histone H1 phosphorylation compared to MIH alone. Thus, the study showed that prior incubation with melatonin could accelerate the action of MIH on oocyte maturation[4] (Figure 2).

4.1 Mode of Action of Melatonin on the Ovary

4.1.1 Melatonin Actions on the Ovary via Ovarian Receptors

The direct action of melatonin on ovarian functions gained attention from studies in isolated human oocytes[117] and in rat ovaries[118]. The function of membrane-bound Mel1aR in mediating intracellular effects of melatonin is well understood[77], but the role of cytosolic Mel1aR was unknown until 2009 when melatonin receptors were found in both the membrane and cytosolic fractions of carp ovarian homogenate[114] (Figure 2). The immunoreactivity of Mel1aR protein in the carp ovary is highest at midnight and lowest at midday in a diurnal cycle. The pattern of day-night rhythms in ovarian Mel1aR is not influenced by the fish's reproductive status or changing photo-thermal conditions. The nocturnal pattern of ovarian Mel1aR, on the other hand, varies with fish reproductive stages, with a peak during the spawning phase and lowest during the post-spawning phase[119]. There have been investigations that demonstrated the expression of melatonin receptors in teleost ovaries: MTNR1a, MTNR1b, and MTNR2 protein in the Indian major carp[114,119], MTNR1a, MTNR1b, and MTNR1c mRNA in mudskipper (*Boleophthalmus pectinirostris*)[108] and orange-spotted grouper (*Epinephelus coioides*)[120], MTNR1a and MTNR1c in Nile tilapia (*Oreochromis niloticus*)[121], MTNR1aa and MTNR1ab in Zebrafish (*Danio rerio*)[82] and MTNR1a protein in medaka[122]. These findings suggest the direct effect of

melatonin on the fish ovary by activating the melatonin receptor. However, recent studies revealed that melatonin is produced in the ovary and directly influences ovarian physiology at the ovary level. Therefore, fish oocyte maturation may be aided by the direct effects of locally synthesized melatonin in the ovary.

Studies on a variety of fish (both in tropical and temperate, as well as *in vivo* and *in vitro*) provide evidence that melatonin regulates the various stages of reproduction[83,115]. A recent study on zebrafish (*Danio rerio*)[82] investigated the impact of different photic conditions on the melatonin profile in the brain and ovary, demonstrating their direct role in ovarian physiology, including maturation (Figure 2). The study further investigated the measurement of GVBD; MPF; and the expression of mprb, intra-ovarian growth factors such as transforming growth factor beta-1a or tgfb1a, bone morphogenetic protein 15 or bmp15, and ovarian melatonin receptors (mtnr1aa and mtnr1ab). Numerous studies on tropical carp and zebrafish revealed that melatonin and its receptor in the ovary play a crucial role in accelerating oocyte maturation[83,114,115]. These findings were supported by a recent study in zebrafish[82], which revealed elevated ovarian melatonin levels and its receptor (mtnr1aa and mtnr1ab) under constant darkness conditions. However, the independent melatonin-synthesizing machinery found in the ovary of zebrafish and tropical carp[30,38] suggests that increased local and *de novo* melatonin synthesis in the ovary may enhance oocyte maturation, though their mode of action may differ from other organs (Figure 2). According to Khan *et al.*[38], increased melatonin signals from the brain may be received by the ovarian melatonin receptors coordinating and regulating ovarian melatonin biosynthesis and leading to oocyte maturation. Overall, the highly activated melatonin receptors in the ovary under the condition of constant darkness resulted in a higher percentage of GVBD via a decrease in the abundance of the upper 35-kDa form of Cdc2, with a corresponding accumulation of Cyclin B1, indicating active MPF formation[82] (Figure 2). Moreover, the action of non-pineal melatonin on ovarian physiology was revealed in another study[46] in which, hepatic melatonin was shown to play an important role in seasonal growth and development of oocytes as well as endogenous levels of ovarian steroids in the carp, *Catla catla*. This effect of hepatic melatonin is borne out in a new possibility that might play a role in the process of vitellogenesis in the liver and, thereby, the seasonality of ovarian functions.

4.1.2 Melatonin Actions on the Ovary Independent of Receptors

Melatonin can pass through the cell membrane due to its amphiphilic nature and may act as a highly prevalent direct free radical scavenger and indirect antioxidant[123]. This raises the possibility that, in addition to its receptor-mediated actions, this indoleamine hormone may have a receptor-independent step in regulating several physiological functions, including reproduction[3,124]. Moreover, melatonin can donate electrons to reduce the reactivity of molecules with an unimpaired electron in their valance orbital, i.e., free radicals, allowing it to interact directly with potentially harmful agents without first binding to receptors[125] (Figure 2).

5. Conclusion

The multiple sites where melatonin is produced from tryptophan may indicate diverse functions depending on the tissue/cells in which it is being synthesized, suggesting its physiological importance for cell functions. Surprisingly, the study on fish pineal and retina provides the basis for the belief that both organs/tissues are significant sources of circulating melatonin by showing parallel rhythmic changes in melatonin concentrations in circulation. Although the retina and the pineal share common intracellular photoreception mechanisms, the retina may serve a complementary or supplementary role to the pineal functions, even though the pineal appears to be the primary source of serum melatonin. However, direct evidence of melatonin synthesis in any fish ovary remains controversial; as a result, melatonin detected and measured in the fish ovary casts doubt on its cellular site of synthesis. Moreover, the gastrointestinal tract and the liver are vital sites for melatonin production and release, but their rhythmic characteristics differ. Though melatonin synthesis in the liver is controlled by environmental photothermal cues, melatonin synthesis in the gut is independent of environmental LD conditions, bespeaks a hitherto unknown non-photic circadian function.

The current understanding of the role of melatonin in regulating oocyte growth and maturation in fish is solely

based on melatonin, which is produced endogenously by the pineal organ or added exogenously by injection[4]. The altered amount of physiological melatonin obtained through either photoperiodic modulation or exogenous injection plays a significant role in regulating gonadal activities in fish, resulting in a pro- or anti-gonadal response depending on the reproductive status of the fish[4,29,67,68,72,74,75,80,83,88,114,116,126]. Despite promising data on pineal gland-derived melatonin and being an effective candidate in fish reproduction, this molecule has been facing severe problems in its application in aquaculture over the last decades. Major setbacks in the daily use of melatonin in aquaculture are: (i) struggle in photoperiodic alterations in a fish farm; as an increase in natural day-length needs the additional lighting on the fishpond, which results in added expense for consuming extra electricity, thereby, the entire process is not cost-benefit for the farmer; (ii) reduction of natural photoperiod also requires the covering of pond, which is not a feasible approach in extensive aquaculture, that also hinder the fertility of the fishpond; (iii) exogenous melatonin treatment for consecutive days to each fish is also a very stressful practice that is not feasible to perform regularly in large-scale aquaculture. The price of commercially available melatonin is also a matter of concern[58]. Hence, melatonin has never been implemented in large-scale aquaculture despite being a potent candidate for regulating fish reproduction. Recently, at least two reports were documented, indicating that the oral supplementation of melatonin also has a significant effect on reproductive functions in fish species[86,87]. This invites us to think about the extra-pineal or extra-retinal sources of melatonin, especially those not controlled by photoperiodic regulation, like gut melatonin. Thus, the melatonin synthesized within the gut may be sought under discussion in regulating and manipulating physiological melatonin to exert any effect on oocyte growth and maturation precisely. However, unfortunately, such an experiment-based study is missing in the available literature.

6. Acknowledgements

Financial assistance from the Council of Scientific and Industrial Research (CSIR), Government of India, New Delhi (37(1737)/19/EMR-II) and University of North Bengal (1950/R-2019 and 2309/R-2022) to SM, two Senior Research Fellowships [660/(CSIR-UGC NET JUNE 2019) to SS and 743/(CSIR-UGC NET DEC.2018) to FY] and one Junior Research Fellowship (221610108177 to RS) by UGC, Government of India, are gratefully acknowledged. The authors deeply thank Prof. Saumen Kumar Maitra, Visva-Bharati University, Santiniketan (Retd), for his continuous motivation, generous unconditional support, and academic encouragement. The authors are grateful to the editor and reviewer for their critique and constructive comments on the previous versions of the manuscript.

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