INNOVARE JOURNAL OF SCIENCES

Vol 7, Issue 3, 2019 ISSN - 2321-5496

Review Article

THE FUNCTIONAL ROLE OF MELATONIN AND KISSPEPTIN IN FISH REPRODUCTION

PRADIP MONDAL, SUMIT KUMAR HIRA, NIMAI CHANDRA SAHA*

Department of Zoology, The University of Burdwan, Burdwan, West Bengal, India. Email: sahanvcbu@gmail.com

Received: 11 May 2019, Revised and Accepted: 30 May 2019

ABSTRACT

Reproduction of fish generally governed by the counter interaction of some endogenous and exogenous cues such as endocrine signals and one or more environmental factors such as photoperiod, temperature, rainfall, food availability, and salinity. Study indicates that it depends on the hypothalamo-hypophysis-gonadal axis. In gonad, gametogenesis is ordered by various hormones followed by their interactions with proper tissues leading to breed at a specific time of the year. Melatonin, a neuroendocrine hormone, has a significant physiological role in the regulation of seasonality and gonadal development of fish. On the other hand, receptor-independent actions or free radical scavenging role of melatonin at different levels of the hypothalamo-hypophysis-gonadal axis is not yet clear. In recent years, the focus has been given to study of the kisspeptin peptides potentiality on gonadal development, especially during the transitional period of puberty and gonadal relapse. The relationship between kisspeptin and gonadotropin-releasing hormone is a good illustration of the kisspeptin system. The role of kisspeptin and melatonin in the reproduction of fish is an important subject of research. The potency of kisspeptin and melatonin on reproductive maturation and gonadotropin release in response to environmental cues and the regulation of secretion of gonadotropin-releasing hormone by kisspeptin and melatonin are also the important objectives of the present review.

Keywords: Environmental cues, Fish, Gonadotropin-releasing hormone, Kisspeptin, Melatonin, Reproduction.

INTRODUCTION

The daily and seasonal cycles in local environments are created by the tidally locked binary rotational system of earth and the sun in an elliptical pathway. The totality of life and its chronology of biological systems have been evolved and regulated by these cosmological phenomena. The differences in environment between winter and summer, monsoon, and spring are dramatic on our planet. The environment has significant effects on living organisms and governs them to adapt and overshoot the natural selection pressures through hibernation, aestivation, diapauses, migration, mimicry, and reproduction. Such contrasting environmental influence allows the individual to sustain and reproduce successfully at the critical time of the year. Hence, the individual must constitutionally know the optimum time of year and prophesy of the upcoming environmental alteration as it needs several days to complete the changes in body physiology [1].

During evolution, the animals have developed several mechanisms to adapt themselves in the altered environmental condition in response to the stimuli associated with environmental changes in day-length, temperature variations, and the preparedness of an organism to redesign adequately to its internal changes and energy requirements. The activities of different neurotransmitter-like substances and hormones of the animals operate on the daily and annual cycle fluctuations and help them to determine their respective adaptive behavior and synchronize them with the environment. The coinciding of environmental and physiological phenomena plays the key role in fish neuroendocrine system consisting of different sensors and oscillators such as the suprachiasmatic nuclei of the hypothalamus, pineal organ, and lateral eyes [2].

External environmental factors like photoperiod, temperature, rainfall, salinity influence the sexual maturation and gonadal development of fish. Earlier studies indicate that the pineal organ translates the environmental (photoperiodic and thermal) signal into rhythmic changes of hormonal oscillations, and the pineal complex can be considered as the major circadian pacemaker [3]. The serum and pineal melatonin (*N*-acetyl-5-methoxytryptamine) level in animals are directly correlated with the duration of night. The report indicates that the removal of the pineal gland in fish inhibits their seasonal reproductive cycle [4]. It seems that melatonin suppresses hypothalamus-pituitary-gonadal (HPG) axis to regulate the reproduction of fish. However, the route of melatonin action in this process is not clearly known [5].

Melatonin regulates fish reproduction in different ways. Melatonin may affect the kisspeptin and gonadotrophin-releasing hormone (GnRH) expression. The KissR-like sequence or gene expression first identified in GnRH neurons from Nile tilapia (*Oreochromis niloticus*) and teleost like zebrafish (*Danio rerio*) justifies the specific role of kisspeptin in fish brain [6]. Melatonin treatment increases kiss2 gene expression in zebrafish [7]. On the other hand, melatonin regulates kiss and GnRH expressions in sea bass [8]. Kisspeptin is now considered to be an essential regulator of the HPG axis in fish species. It is reported that the kisspeptin binds to its orphan G-protein-coupled receptor-54 in several fish species [9]. The report is also available on the role of kisspeptin-Kiss R signaling in reproduction, particularly the control of GnRH-luteinizing hormone (LH) secretion during the onset of puberty in mammals [10]. Numerous studies have demonstrated the role of kisspeptin governing the reproductive physiology in mammals and also in fish species [11]. However, the knowledge on non-hypothalamic kisspeptin–Kiss R system is scanty [12].

The present review summarizes the study on the kisspeptin peptides and melatonin on maturation of fish leading to reproduction. The review will help in basic understanding of fish physiology needed for scientific aquaculture and stock management. The study will strengthen the existing information on the role of the kisspeptin peptides and melatonin on fish reproduction.

MELATONIN AND FISH REPRODUCTION

Female fish

Melatonin, the indoleamine affects female fish reproduction through the hypothalamus, pituitary, and ovary through the hypothalamo-hypophyseal gonadal axis through receptor-mediated or receptor-independent direct actions [13]. The final process of oocyte maturation is promoted by maturation-inducing hormone (MIH) that elicit to the formation of maturation-promoting factor (MPF) inside the cytoplasm of the oocyte. Melatonin is well known as an inducer of MPF and enhances the functionality of MIH when it is added 4 h before MIH addition to the incubation medium [14]. The pretreated with melatonin, MIH showed an increase cyclin B level continued to even after 4 h and showed amplitude after 12 h of incubation. One of the major indicators, the H1 kinase of MPF complex in oocytes became higher and indicated that pre-incubation with melatonin enhanced MIH stimulation of H1 (histone) phosphorylation as compared to MIH solemnly. This report supports the extra-hypothalamic action of melatonin on oocyte maturation in fish species [14]. It has been found that exogenously treated melatonin helps to elevate the intraovarian melatonin, which ultimately stimulates endogenous antioxidants to minimize the oxidative stress in carp ovary. In addition to that, the exogenous melatonin has also progonadal effect in the preparatory phase and antigonadal effect during prespawning or spawning phases of reproductive development [15]. A previous study on zebrafish (*D. rerio*) reported that melatonin has a direct action on follicles (increase of germinal vesicle break down [GVBD]) modulating *mpr* α and β gene product (important for oocyte maturation) expression [7]. It is also reported that the incubation of oocytes with serotonin (precursor of melatonin) or melatonin or both serotonin and melatonin diminish the stimulatory effect of melatonin and MIH on the rate of GVBD [16]. Melatonin is *de novo* synthesized in the zebrafish ovary, and its interaction with the brain involves clock-associated genes controlling rhythmic regulation of reproduction [17]. The effect of altered light in zebrafish (*D. rerio*), the result revealed a clear desynchronization of clock associated genes and development of an ovarian tumor. The upregulation of different genes associated with tumorigenesis and ultimately increases the expression of nuclear factor-kappa B (NF-κB) protein, a cellular transformer for tumor revealed in above ovarian samples. The appearance of tumor necrosis factor-α, inflammatory cytokines, and activator of NF-κB also increased. The thecoma and granulosa cell tumor appeared in 1 year exposed fish to artificial light at night in the ovarian sample [18]. The pathways governed by melatonin regulating reproductive seasonality of ovarian physiology and its influence on antioxidant enzymes in natural and altered environmental conditions on fish ovary is not clearly known till date (Fig. 1).

Male fish

A clear and high negative significant correlation present between the epiphysis cerebri and the male germ cell during the four distinct phases (preparatory, prespawning, spawning, and postspawning) of the annual reproductive cycle of carp [19]. The photoperiod has a great role in the maturation of gonad of year old precocious male masu salmon (*Oncorhynchus masou*). Gonadal development accelerated by a short photoperiod (light-dark cycles of 8:16 h; LD 8:16) and delayed by a long photoperiod (LD 16:8). Circulating melatonin levels are high during the night and low during the day. It is reported that fish reared under LD 16:8 (lights on 04:00–20:00 h) and fed pellets sprayed with melatonin (0.5 mg melatonin/kg body weight/day) or vehicle once a day at 11:00 h for 4 months faced a stimulatory effect followed by higher levels of gonadosomatic index (GSI), pituitary gonadotropin hormone (GTH),

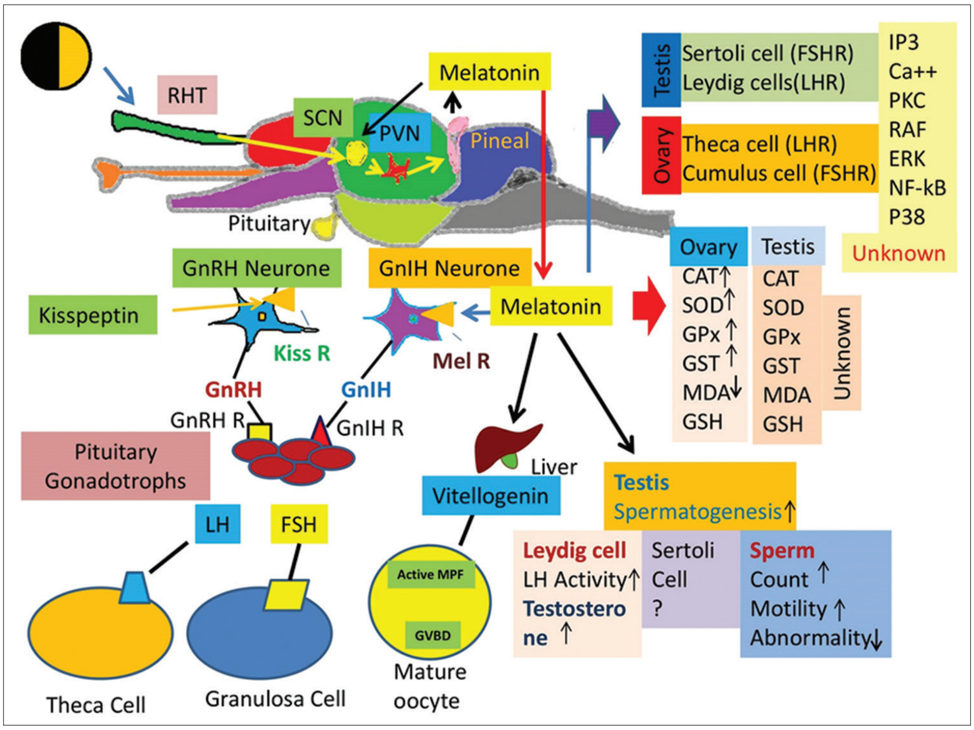

Fig. 1: Diagrammatic representation of the gathered information from the previous studies on different fish species to describe the presumptive role of melatonin and kisspeptin in the regulation of fish reproduction. Photoperiodic stimuli perceived through eye, transmitted through the retinohypothalamic tract, through a complex pathway involving suprachiasmatic nuclei, paraventricular nuclei, and to the pineal gland. Melatonin once released into the blood, acts on the hypothalamo–hypophyseal–gonadal (hypothalamus-pituitary-gonadal) axis to regulate oocyte development. Melatonin function on gonadotropin-inhibitory hormone neuron and downregulate the folliculotrophs in the pituitary as well as gonads, whereas kisspeptin acts on gonadotrophin-releasing hormone neuron and upregulates the gonadotrophs cells in the pituitary. Melatonin may directly acts on liver and regulates vitellogenesis, which then ultimately stored into the mature follicle. Melatonin also acts on the ovary and promote maturation promoting factor, to induce final maturation and govern germinal vesicle break down. On the other hand, melatonin action on testis may increase the sperm count, motility, the activity testosterone, and decrease the abnormality of sperm. Melatonin action increases the activity of follicle-stimulating hormone and luteinizing hormone on Sertoli and Leydig cells, respectively. The antioxidative function of melatonin is partially understood in fish ovary, where exogenous melatonin has increased the level of superoxide dismutase, catalase, glutathione peroxidase, glutathione S-transferase, and decreases the malondialdehyde level. However, the signaling mechanism is not yet understood. Antioxidative action on fish testis is not yet clear. Abbreviations: Inositol-tri-phosphate (IP3), Calcium (Ca^{++}), Protein Kinase C and signaling protein RAF, ERK, nuclear factor–kappa B, P38

and plasma testosterone [20]. However, no significant differences were observed in GTH II contents in the pituitary during spermiation in fish exposed to long and short photoperiod. It suggests that mimicking a short photoperiod by melatonin stimulated testicular development cannot completely activate the brain-pituitary-gonadal axis in precocious male masu salmon. It indicates that melatonin is one of the effective agents that mediate the luminal transduction of photoperiod through the brain-pituitary-gonadal axis [20]. Spermatogenic or sperm-producing activity is stimulated by this indoleamine by increasing the sensitivity of Leydig cells to LH or GTH II. Besides enhancing the maturation through pituitary-hypothalamus-gonad axis, melatonin also acts directly on the testes through Leydig cells. Therefore, GTH-II regulates Leydig cell sex steroid production, such as testosterone [21]. Testosterone is essential for spermatogenesis in the testis. The testosterone has the capacity to increase sperm quality by inhibiting the apoptosis of spermatocyte and spermatide. The feeding with melatonin to male *Clarias macrocephalus* showed improved puberty by enhancing the maturation of testes and sperm. Earlier studies showed that melatonin enhances the male reproductive system leading to more efficient gamete management with an increased yield of catfish [21]. The review showed that the knowledge on melatonin action as hormone and antioxidant in male gonad of fish is still limited provides scope for further research (Fig. 1).

Effects of environmental factors in the regulation of melatonin synthesis

The biological rhythm in all vertebrates centrally controlled by HPG axis and pineal gland and environmentally by photoperiod and circadian axis, which is based on a circadian pacemaker mechanism [2]. The entraining light signals from photoreceptors are turned into neuroendocrinological signals that subsequently transmit this information into target tissues to determine the physiological responses and rhythms. In lower vertebrates, the majority of circulating melatonin is produced by the pineal gland and some amount is produced by the retina. Although melatonin is the main endocrine signal transducer molecule regulated by environment and photoperiod through retina-hypothalamic tract [22]. Pineal organ appears to have undergone a clear transformation from being primarily a sensory organ in the lower group of vertebrates to a major endocrine gland in birds and mammals and perform sensory, secretory, and protective functions [2]. Arylalkylamine-*N*-acetyltransferase, the rate-limiting enzyme in the melatonin biosynthetic pathway, is a photosensitive protein that determines melatonin rhythms in the pineal organ in a number of fish species [23]. The fish pineal is a photoreceptive organ that percept the light stimuli from the environment and conveys this physical message into a chemical signal by varying the amount of melatonin synthesis which ultimately correlates the activity of the animals with the conditions of the external environment. It is more important that the melatoninergic system in Indian major carp also depends on the external photoperiodic conditions, in addition to the endogenous circadian oscillator in the pineal. The regulation of melatonin synthesis depends on the circadian axis and may differ from species to species [13]. According to the previous study, we may say that environmental photoperiods are an essential regulator of the melatonin synthesis. However, there are no such satisfactory findings on the other parameters (temperature, salinity, etc.) of the environment for controlling the melatonin synthesis. Hence, there is an open space for further research to find out the regulation of melatonin synthesis by other environmental factor other than light.

Receptor-dependent action of melatonin in fish reproduction

Presence of melatonin receptors in isolated mammalian oocytes gives a definite idea of the direct effect of melatonin in the regulation of ovarian function [24]. However, no such information of melatonin receptors in fish gonads was available until the work of Chattoraj *et al.* (2009) [25]. This study reports on the localization of melatonin receptors in different cellular fractions of the ovary as well as their diurnal profiles in different parts of an annual reproductive cycle [25]. These receptor proteins are detected in both the membrane and cytosolic fractions of the carp ovarian homogenate. The ovarian Mel1a receptor is always showed higher expression in the membrane fraction than in its cytosolic counterpart. It is well understood that the function of membrane-bound Mel1aR in the mediation of intra-cellular effects. However, the occurrence and significance of cytosolic Mel1aR remain obscure. The nocturnal expression of Mel1aR within the ovaries differs in relation to the reproductive phases of their reproductive cycle. Expression reaches highest during the spawning phase and becomes lowest during the post-spawning phase. The diurnal peak value of serum melatonin showed in the late dark phase and ovarian Mel1aR showed at midnight. There is a significant positive correlation found between the serum melatonin and Mel1aR in the ovary of carp in each reproductive phase [26]. It is reported that the daily administration of melatonin at the rate of 25 μg/100 g body wt for 30 days in male (19) and female (27) carp leads to a pro-gonadal response during the preparatory phase but showed anti-gonadal activity in prespawning and spawning phase, but no response was recorded in the post-spawning phase of the reproductive cycle. It is also assumed that exogenous melatonin on gonads in carp might be related to the reproductive phase-dependent effects. The melatonin receptors in the carp ovary obviously contribute to the mechanism of melatonin action on gonadal maturation and GVBD and ultimately interactions with other biomolecules in the regulation of fish reproduction [13]. Further studies are needed to justify this hypothesis. Proper modeling is required to know the relationship between the rhythmic patterns of melatonin and its receptors on the ovary with the photoperiodic response. The information and the available data on the melatonin receptor's dynamics and localization in the carp oocytes offer interesting perspectives to explain the control mechanisms of its rhythm and response to external cues. In the perspective of information, it appears that the results of the previous study obtained in carp might permit a view into the physiology of melatonin in the reproductive control of fish [15,27].

Receptor-independent action of melatonin in fish reproduction

The melatonin is lipophilic in nature. It can easily cross the plasma membrane of any cell and may work as a direct free radical scavenger [28]. This indoleamine plays a critical role into the development of defense against oxidative stress by enhancing different antioxidant enzyme system in different tissues, including those present in the reproductive system [29]. Some previous reports on mammalian studies found that melatonin and even its metabolic byproduct may also act as a potent antioxidant in the regulation of ovarian activity [30]. It is reported that the generation of overproduction of free-radical occurs during ovulation process resulting the elevated level of oxidative stress and ultimately affects ovarian activity [29]. Melatonin levels also synchronize with the development of follicular growth and it has a novel physiological significance in ovulation. Melatonin has the capability to minimize free-radical damage in the oocyte by scavenging the free-radical and ultimately improve the quality of oocytes [29]. The melatonin also functions as an antioxidant by activating antioxidative enzymes such as catalase, superoxide dismutase, and glutathione peroxidase, which metabolize free radicals to minimizes oxidative stress in mammalian *in vivo* on different cells of ovarian follicles [30]. It is documented that this indolamine has an important function in the metabolic pathway of oocyte maturation by protecting oocytes against free radicals in the mammalian preovulatory follicles [30]. Such data on fish are scanty. A seasonal study on adult carp held under natural photo-thermal conditions demonstrate that melatonin acts as an antioxidative agent in reducing oxidative stress to felicitate ovarian functions during the spawning phase [31]. Study on carp showed that melatonin actions on ovaprim (synthetic GnRH and domperidone)-induced oocyte maturation promotes an idea that melatonin pre-treatment alleviates oxidative stress of preovulatory follicles by activating different antioxidants and regulates ovaprim actions on the process of final oocyte maturation [26]. It is well documented that carp treated with the same dose regimen of melatonin in various phases of the reproductive cycle showed a correlation between ovarian melatonin, different antioxidants, and different stages of growing oocytes. That finding proves that melatonin is an essential antioxidant candidate and reduced stress in the regulatory pathway of seasonal growth and development of the ovary. Findings also support that melatonin treatment elevates intraovarian melatonin titers, which elicit endogenously available antioxidants and reduce oxidative stress in the carp ovary irrespective of seasons throughout the annual reproductive cycle. Under identical dosage regimen, exogenous melatonin regulates the growth of oocyte by accelerating (during preparatory phase) or retarding (during prespawning or spawning phases) perspective [15] (Fig. 1).

Future prospect of melatonin in aquaculture

As we have seen earlier melatonin has the effectiveness for reduced oxidative stress and promotes the oocyte quality in fish; this molecule is one of the most promising in the fields of fish culture. Melatonin is one of the nature's most well-known potent antioxidant may act locally to reduce oxidative stress in the ovary. Extensive research is needed to prove the mechanistic pathway involved in the regulation of HPG axis from the environment to gonad. Thus, it may be helpful for the aquaculture industry in different means such as induced breeding.

KISSPEPTIN AND FISH REPRODUCTION

GnRH neuron cell bodies and Kisspeptin fibers are closely associated in the brain. A number of GnRH neurons express Kiss1R mRNA, which indicates that kisspeptin neurons directly transmit a signal to the GnRH neurons. The administration of Kisspeptin10 peptide was found to enhance the circulating levels of GnRH [32]. The kisspeptin signaling through GnRH for the onset of puberty and ovulation is observed in mammals. The existence of a kisspeptin system in fish was recorded by early workers through isolation of the complementary DNA (cDNA) of the kisspeptin receptor (KissR2) in Nile tilapia (*O. niloticus*) [33]. One kisspeptin gene (Kiss1) coding for the ligand and one for the receptor (Kiss1R) were found in mammals. Most of the fish have only two receptors, kissr2 and kissr3 (also known as G protein receptor [GPR]54-1b and GPR54-2b) but two kisspeptin genes (*kiss1 and kiss2*) and four kisspeptin receptors gene were also reported in teleost [34]. In the brains of all vertebrate species, two forms of GnRH are available. In some teleost, three different forms of GnRH (i.e., GnRH1, GnRH2, and GnRH3) are expressed. A teleost-specific form GnRH3 expressed in the olfactory bulb, terminal nerve ganglion region, and the pre-optic area. The GnRH3 axonal fibers projecting into different regions of the brain suggest a role in neuromodulation and secretion of pituitary gonadotropins [20]. Hence, the core underlying query is that kisspeptin an effective regulator of the reproductive brain-pituitary-gonad (BPG) axis in fish or not. In cichlid fish (e.g., *O. niloticus* and *Astatotilapia burtoni*) and striped bass (*Morone saxatilis*) the GnRH1 neurons express kissr2 mRNA indicating the expression of kisspeptin receptor in the hypothalamus [35]. Previous studies have shown that the secretion of GnRH and gonadotropins are promoted by the injection of Kiss2 peptide [36]. It is reported that antagonists of kisspeptin prohibit male germ cell production in striped bass [35]. Knockout mutants in kiss receptor exhibit normal gonadal maturation in zebrafish (*D. rerio*), which indicates that kisspeptin signaling is not essential for reproduction in zebrafish [37]. Some reports indicate that kisspeptin receptors are not expressed in GnRH neurons in medaka (*Oryzias latipes*) or European sea bass (*Dicentrarchus labrax*) [38]. Therefore, the actual role of kisspeptin in reproduction remains open for further research in fish. The available data on the mechanism of reproductive regulation in teleost vary greatly within a species, may be due to the variable evolutionary background, species diversification, reproductive style, and ecological niches. The non-model fishes may also support to understand the mechanisms underlying within reproductive physiology of fish. In recent years, the study focused on the potency of kisspeptin peptides in gonadal development, pubertal transition period, and gonadal recrudescence, which is important for the establishment of successful aquaculture of any fish edible species [39].

Kisspeptin regulation by an environmental factor

Animals inhabiting in temperate climates experience strong seasonal fluctuations in environmental factors that influence survival and reproductive success. To cope up with these fluctuations, individuals have evolved controlling mechanism of reproduction to times of the year when conditions are most favorable for the survival of self and offspring. Earlier reports indicate that the environmental cues may be of two types: The initial predictive cues that signal the likelihood of future energy availability (e.g., photoperiod) and supplementary cues that are direct indicators of immediate energy availability (e.g., current food availability). Reports showed that exogenous kisspeptin to hamsters initiating gonadal regression when exposed to combinations of photoperiodic and food availability. Exogenous kisspeptin also showed that it did not block the normal process of gonadal regression when it administered alone in hamster [40]. Therefore, it has been hypothesized that exogenous kisspeptin would be successful in blocking regression in response to the supplementary cue of food restriction in an intermediate photoperiod. Therefore, it demonstrates that the integration of photoperiodic and food availability cues to organize appropriate reproductive responses in complex environmental conditions [41]. To examine the functional role of kisspeptin in driving reproductive responses to environmental cues such as changes in energy availability, scientists showed that it inhibits the process of gonadal regression in male Siberian hamsters [41]. The previous study predicts that exogenous kisspeptin treatment has the capability to preserve reproductive physiology and endocrine function. In such environments, in which hamsters are solely reliant on supplementary cues such as food restriction and intermediate photoperiod, but exogenous kisspeptin becomes nonfunctional to overshoot environmental conditions that strongly inhibit reproduction like short-day photoperiod [36]. Experimental reports assume that the possible mechanism by which kisspeptin may regulate reproduction in response to the environment through maintaining activation of the HPG axis in inhibitory environments. The activations of the HPG axis at the pituitary and gonadal level are determined by circulating LH and testosterone concentrations. Previous findings demonstrated that a strong relationship is found between the environmental control of puberty, Kiss1, and GnRH 2 systems in European sea bass. Photoperiod modulates the expression of kiss1 and GnRH 2 in the brain, which may be involved in the translation of light stimuli to activate the reproductive axis. Therefore, it is well documented that the photoperiodic schedule is able to alter hormone profiles and ultimately regulates the onset and progression of the whole process of gametogenesis [36]. It is obvious that further research is needed to establish the pathway by which environment regulate the kisspeptin synthesis, which ultimately regulates the fish reproduction (Fig. 2).

Upstream and downstream regulation of kisspeptin associated with fish reproduction

It is well defined that kisspeptin neurons play an essential role in the regulation of reproductive function [42]. The environmental factor like scarcity of food in mammals decreases hypothalamic kiss1which transmitting metabolic information to the GnRH network [43]. The kisspeptin system in metabolic regulation of the BPG axis is scanty in fish. Some findings showed that the interactions between nutrition and reproduction in the European sea bass (*D. labrax*). The influence of long-term restriction in feeding, male European sea bass started their first breeding season [38]. It is noticeable that restriction of food in sea bass delay gonadal development and resulted in a low GSI may be due to the increase in the number of apoptosis in the germ cells of the testes [38]. In some cases, a food restriction regime actually increases key sperm motility measurements [38]. The study showed that fasting increases hypothalamic kiss2 expression; in turn, lhβ and follicle-stimulating hormone β (FSHβ) mRNA levels in the pituitary of male and female fish [44]. FSH plays a major role in early spermatogenesis, when testicular growth occurs actively [45], whereas LH has been involved in the final stages of testicular growth and maturation in sea bass [46]. A collaborative role of both gonadotropins in improving testicular function has also been suggested in this species [36]. The study demonstrates that the long-term food restriction affects kisspeptin genes, other reproductive hormones and factors involved in the BPG axis of male European sea bass over the course of their first reproductive cycle (puberty) (Fig. 2).

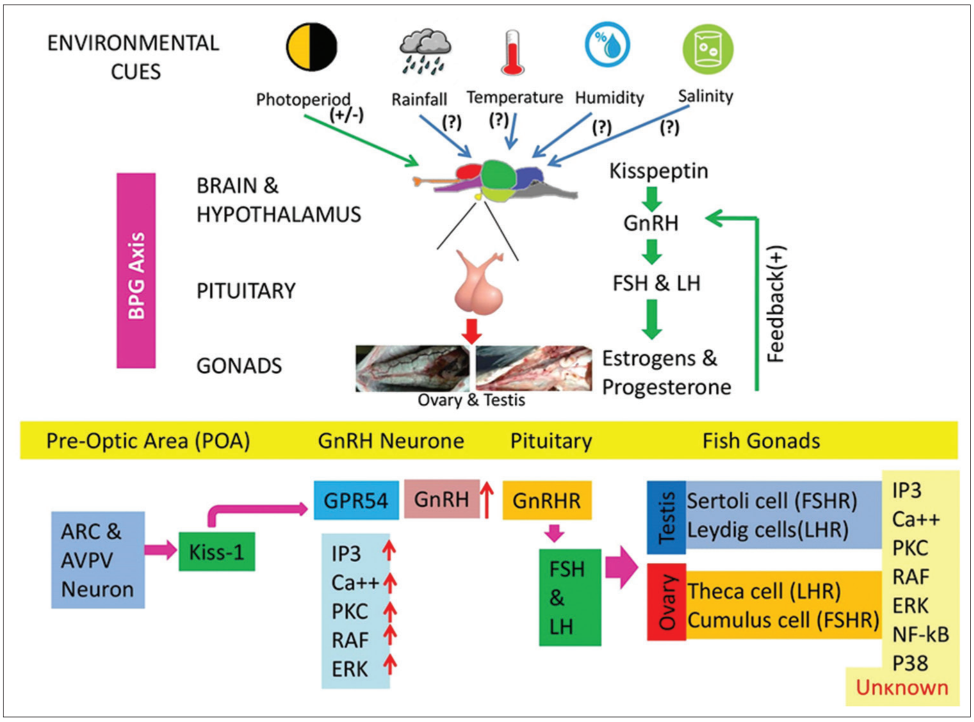

Fig. 2: Schematic representation of the information collected from the previous studies on the role of kisspeptin in the regulation of fish reproduction and its relationship with the environment. Photoperiodic stimuli and transmitted through the retinohypothalamic tract, through a complex pathway into the kisspeptin nucleus, which is closely associated with gonadotropin-releasing hormone (GnRH) neuron in the hypothalamus. Kisspeptin function on GnRH neuron and upregulate the folliculotrophs in the pituitary as well as gonads. The signaling pathway associated with the kisspeptin in the gonads cells (Leydig and Sertoli, theca, and granulosa cells) is not yet clear. Only a few reports are there to regulate the kisspeptin by environmental stimuli such as photoperiodic regulation but temperature, humidity, and salinity and the effects of rainfall are still yet to uncover. Abbreviations: Arcuate nucleus (ARC), anteroventral periventricular nucleus, G protein receptor 54 inositol-triphosphate, Calcium (Ca^{++}), protein kinase C, and signaling protein RAF, ERK, nuclear factor-kappa B, P38

Future prospect of kisspeptin in aquaculture

The previous insights on fish kisspeptin physiology study a message that the kisspeptin system plays a key role in the reproductive success of many fish species through various known or unknown neuronal networks. It must be noted that the methods involved differ from species to species. The correlation between kisspeptin and GnRH neurons is really important of the high species specificity of the kisspeptin system. According to the previous discussion, it may satisfy that fish kisspeptin is a central and absolute upstream regulator of the GnRH–GTH pathway as is the case in mammals. Whereas fish are known as the earliest vertebrates, and it may be that their hierarchical reproductive fine network has not yet been completed. Therefore, further extensive research required for establishing the absolute role of kisspeptin in fish reproduction [39].

SYNERGIC EFFECT OF MELATONIN AND KISSPEPTIN IN FISH REPRODUCTIVE REGULATION

The potential effects of melatonin in the hypothalamus and dorsal brain were explored by investigating the temporal changes in the expression levels of gene *kiss* and GnRH, their receptors and gonadotropin. Reports demonstrate that melatonin exhibits two distinct effects on the central system. First one, it shows an inhibitory effect on the mRNA expression of kiss1, kiss2, GnRH -1, and GnRH -3 genes of the dorsal brain and second one is the alterations in the hypothalamus. Thus, melatonin action decreases the expression of kiss1 and kiss2 genes in the dorsal brain, which might diminish the gene expression of GnRH forms (GnRH -1 and GnRH -3) and downregulate the expression profiles of different GnRH receptor gene in the pituitary [47]. It was also documented that the exogenous melatonin in sea bass effected the expression of other GnRH receptor forms [47]. The GnRH receptors variation with the day-night cycle helps to understand these systems possibility to mediate photoperiodic effects on the reproduction of fish. Reports also show that after melatonin administration in adult zebrafish female kiss1, kiss2, and GnRH -3 mRNA levels increased. It gives a clear idea about the capability of this hormone to promote follicle maturation and increase of zebrafish fecundity [7]. Therefore, the variation in the impact of melatonin action on brain and gonad observed fish indicates species-specific responses of this hormone. The distribution of melatonin receptor-expression does not match the GnRH -1 and GnRH -3 expressing cells in sea bass [48]. On the other hand, the distribution of kisspeptin neurons does not match GnRH neurons. Kisspeptin receptors are localized in a variety of neurons except in GnRH neurons [38]. Therefore, melatonin may have an indirect influence in both kisspeptin and GnRH neural activities by interneuron [47]. This may happen due to interneuron networks in the dorsal brain coordinating melatonin action between the distinct brain nuclei to elucidate this hormone, which is also act on the hypothalamus. The GnRH -1 fibers are reaching to the pituitary area where gonadotropin cells and GnRH receptors have been found in sea bass [49]. In the orange-spotted grouper, it is considered that the expression of the melatonin receptor MT1 subtype down-regulation may upregulate GnRH -1 expression through an increase in kiss2, probably by this kiss form responsible for regulating reproduction in this species [50]. This hormone induces changes that affect gonadal development in adult sea bass if administered over an extended period of time throughout their entire reproductive cycle. Although the pathway of melatonin action is still unknown in sea bass, molecular evidences present on its effect at the brain level, including the hypothalamus and the dorsal brain, were observed. The previous finding shows that the possibility of melatonin presumably induces the downregulation of kisspeptin-GnRH on the dorsal brain, which might affect fhsβ expression at the pituitary level during early gametogenesis and provoke disturbances in the testicular development of sea bass [8]. The study provides the first step looking at the effects of pineal removal on gonadotropin-inhibitory hormone

(GnIH), kisspeptin, and GnRH systems in fish. The results demonstrated that GnIH localized in the mid-hindbrain region and showed sensitivity to pinealectomy suggesting that it may be involved in perceiving and integrating photoperiod information, while the diencephalic population of GnIH showed clear seasonal expression. A key finding is a difference in dynamics observed between the different GnIH populations which are likely to reflect varied functional roles. This stresses the importance of future regional studies to help shed light on the functions of each GnIH population. The effect of pinealectomy on diencephalic GnIH, kisspeptin and GnRH system expression, it is difficult to conclude at this stage, on the role of a direct link between photoperiod and reproduction and/or in a pineal-independent manner. The strong seasonal expression of diencephalic GnIH and its receptor, GnRH 2 and kissr3 genes suggest that they are likely to contribute in the seasonal shift of environmental cues to a physiological change in reproduction in fish [51]. In the future, combined pinealectomy, ophthalmectomy and melatonin implant studies as well as melatonin pharmacological and circadian rhythm studies on these neuropeptide systems of interest should help to unravel information on their potential involvement in the transduction of photoperiod information to reproductive physiology.

CONCLUSION

The present study indicates a road map to the future researchers to find out the role of kisspeptin as an upstream and melatonin as a downstream regulator of GnRH secretion during the gonadal maturation and reproduction of fish. This review also provides an idea on the potency of kisspeptin and melatonin on reproductive maturation and gonadotropin release in response to environmental cues (photoperiod and temperature). Further intensive research is required to contribute in science, which may be helpful to draw the knowledge from lab to aquaculture industry.

ACKNOWLEDGMENTS

We are thankful to the Department of Zoology, The University of Burdwan for providing the infrastructural facilities and necessary financial support.

REFERENCES

1. West AC, Wood SH. Seasonal physiology: Making the future a thing of the past. Curr Opin Physiol 2018;5:1-8.
2. Falcón J, Migaud H, Muñoz-Cueto JA, Carrillo M. Current knowledge on the melatonin system in teleost fish. Gen Comp Endocrinol 2010;165:469-82.
3. Brüning A, Kloas W, Preuer T, Hölker F. Influence of artificially induced light pollution on the hormone system of two common fish species, perch and roach, in a rural habitat. Conserv Physiol 2018;6:coy016.
4. Kang SW, Thayananuphat A, Bakken T, El Halawani ME. Dopamine-melatonin neurons in the avian hypothalamus controlling seasonal reproduction. Neuroscience 2007;150:223-33.
5. Kim JH, Park JW, Jin YH, Kim DJ, Kwon YJ. Effect of melatonin on GnIH precursor gene expression in Nile tilapia, *Oreochromis niloticus*. Biol Rhythm Res 2017. Doi: 10.1080/09291016.2017.1357336.
6. Comninos AN, Wall MB, Demetriou L, Shah AJ, Clarke SA, Narayanaswamy S, *et al.* Kisspeptin modulates sexual and emotional brain processing in humans. J Clin Invest 2017;127:709-19.
7. Carnevali O, Gioacchini G, Maradonna F, Olivotto I, Migliarini B. Melatonin induces follicle maturation in *Danio rerio*. PLoS One 2011;6:e19978.
8. Alvarado MV, Servili A, Molés G, Gueguen MM, Carrillo M, Kah O, *et al.* Actions of sex steroids on kisspeptin expression and other reproduction-related genes in the brain of the teleost fish European sea bass. J Exp Biol 2016;219:3353-65.
9. Ohtaki T, Shintani Y, Honda S, Matsumoto H, Hori A, Kanehashi K, *et al.* Metastasis suppressor gene kiSS-1 encodes peptide ligand of a G-protein-coupled receptor. Nature 2001;411:613-7.
10. Seminara SB, Messager S, Chatzidaki EE, Thresher RR, Acierno JS Jr., Shagoury JK, *et al.* The GPR54 gene as a regulator of puberty. N Engl J Med 2003;349:1614-27.
11. Loganathan K, Moriya S, Parhar IS. Trek2a regulates gnrh3 expression under control of melatonin receptor Mt1 and a2-adrenoceptor. Biochem Biophys Res Commun 2018;496:927-33.
12. Ogawa S, Parhar IS. Biological significance of kisspeptin-kiss 1 receptor signaling in the habenula of teleost species. Front Endocrinol (Lausanne) 2018;9:222.
13. Maitra SK, Chattoraj A, Mukherjee S, Moniruzzaman M. Melatonin: A potent candidate in the regulation of fish oocyte growth and maturation. Gen Comp Endocrinol 2013;181:215-22.
14. Chattoraj A, Bhattacharyya S, Basu D, Bhattacharya S, Bhattacharya S, Maitra SK, *et al.* Melatonin accelerates maturation inducing hormone (MIH): Induced oocyte maturation in carps. Gen Comp Endocrinol 2005;140:145-55.
15. Mondal P, Hasan KN, Pal PK, Maitra SK. Influences of exogenous melatonin on the oocyte growth and oxidative status of ovary during different reproductive phases of an annual cycle in carp *Catla catla*. Theriogenology 2017;87:349-59.
16. Maitra SK, Hasan KN. The role of melatonin as a hormone and an antioxidant in the control of fish reproduction. Front Endocrinol (Lausanne) 2016;7:38.
17. Yumnamcha T, Khan ZA, Rajiv C, Devi SD, Mondal G, Sanjita Devi H, *et al.* Interaction of melatonin and gonadotropin-inhibitory hormone on the zebrafish brain-pituitary-reproductive axis. Mol Reprod Dev 2017;84:389-400.
18. Khan ZA, Labala RK, Yumnamcha T, Devi SD, Mondal G, Sanjita Devi H, *et al.* Artificial light at night (ALAN), an alarm to ovarian physiology: A study of possible chronodisruption on zebrafish (*Danio rerio*). Sci Total Environ 2018;628-629:1407-21.
19. Bhattacharya S, Chattoraj A, Maitra SK. Melatonin in the regulation of annual testicular events in carp *Catla catla*: Evidence from the studies on the effects of exogenous melatonin, continuous light, and continuous darkness. Chronobiol Int 2007;24:629-50.
20. Amano M, Iigo M, Ikuta K, Kitamura S, Yamada H, Yamamori K, *et al.* Roles of melatonin in gonadal maturation of underyearling precocious male masu salmon. Gen Comp Endocrinol 2000;120:190-7.
21. Aripin SA, Jintasataporn O, Yoonpundh R. Effects of exogenous melatonin in *Clarias macrocephalus* male broodstock first puberty stage. J Aquac Res Dev 2015;6:307.
22. Migaud H, Davie A, Martinez Chavez CC, Al-Khamees S. Evidence for differential photic regulation of pineal melatonin synthesis in teleosts. J Pineal Res 2007;43:327-35.
23. Caskey M, Schoofs T, Gruell H, Settler A, Karagounis T, Kreider EF, *et al.* Antibody 10-1074 suppresses viremia in HIV-1-infected individuals. Nat Med 2017;23:185-91.
24. Soares JM Jr., Masana MI, Erşahin C, Dubocovich ML. Functional melatonin receptors in rat ovaries at various stages of the estrous cycle. J Pharmacol Exp Ther 2003;306:694-702.
25. Chattoraj A, Seth M, Maitra SK. Localization and dynamics of mel(1a) melatonin receptor in the ovary of carp *Catla catla* in relation to serum melatonin levels. Comp Biochem Physiol A Mol Integr Physiol 2009;152:327-33.
26. Moniruzzaman M, Hasan KN, Maitra SK. Melatonin actions on ovaprim (synthetic gnRH and domperidone)-induced oocyte maturation in carp. Reproduction 2016;151:285-96.
27. Maitra SK, Chattoraj A, Bhattacharyya S. Implication of melatonin in oocyte maturation in Indian major carp *Catla catla*. Fish Physiol Biochem 2005;31:201-7.
28. Poeggeler B, Reiter RJ, Tan DX, Chen LD, Manchester LC. Melatonin, hydroxyl radical-mediated oxidative damage, and aging: A hypothesis. J Pineal Res 1993;14:151-68.
29. Reiter RJ, Rosales-Corral SA, Manchester LC, Tan DX. Peripheral reproductive organ health and melatonin: Ready for prime time. Int J Mol Sci 2013;14:7231-72.
30. Tamura H, Takasaki A, Taketani T, Tanabe M, Lee L, Tamura I, *et al.* Melatonin and female reproduction. J Obstet Gynaecol Res 2014;40:1-11.
31. Hasan KN, Moniruzzaman M, Maitra SK. Melatonin concentrations in relation to oxidative status and oocyte dynamics in the ovary during different reproductive phases of an annual cycle in carp *Catla catla*. Theriogenology 2014;82:1173-85.
32. Messager S, Chatzidaki EE, Ma D, Hendrick AG, Zahn D, Dixon J, *et al.* Kisspeptin directly stimulates gonadotropin-releasing hormone release via G protein-coupled receptor 54. Proc Natl Acad Sci U S A 2005;102:1761-6.
33. Parhar IS, Ogawa S, Sakuma Y. Laser-captured single digoxigenin-labeled neurons of gonadotropin-releasing hormone types reveal a novel G protein-coupled receptor (Gpr54) during maturation in cichlid fish. Endocrinology 2004;145:3613-8.
34. Pasquier J, Kamech N, Lafont AG, Vaudry H, Rousseau K, Dufour S, *et al.* Molecular evolution of GPCRs: Kisspeptin/kisspeptin receptors.

J Mol Endocrinol 2014;52:T101-17.
35. Zmora N, Stubblefield JD, Wong TT, Levavi-Sivan B, Millar RP, Zohar Y, *et al.* Kisspeptin antagonists reveal kisspeptin 1 and kisspeptin 2 differential regulation of reproduction in the teleost, *Morone saxatilis*. Biol Reprod 2015;93:76.
36. Espigares F, Rocha A, Gómez A, Carrillo M, Zanuy S. Photoperiod modulates the reproductive axis of European sea bass through regulation of kiss1 and gnrh2 neuronal expression. Gen Comp Endocrinol 2017;240:35-45.
37. Tang H, Liu Y, Luo D, Ogawa S, Yin Y, Li S, *et al.* The kiss/kissr systems are dispensable for zebrafish reproduction: Evidence from gene knockout studies. Endocrinology 2015;156:589-99.
38. Escobar S, Felip A, Zanuy S, Carrillo M. Is the kisspeptin system involved in responses to food restriction in order to preserve reproduction in pubertal male sea bass (*Dicentrarchus labrax*)? Comp Biochem Physiol A Mol Integr Physiol 2016;199:38-46.
39. Ohga H, Selvaraj S, Matsuyama M. The roles of kisspeptin system in the reproductive physiology of fish with special reference to chub mackerel studies as main axis. Front Endocrinol (Lausanne) 2018;9:147.
40. Greives TJ, Kriegsfeld LJ, Demas GE. Exogenous kisspeptin does not alter photoperiod-induced gonadal regression in Siberian hamsters (*Phodopus sungorus*). Gen Comp Endocrinol 2008;156:552-8.
41. Bailey AM, Legan SJ, Demas GE. Exogenous kisspeptin enhances seasonal reproductive function in male Siberian hamsters. Anim Physiol Ecol 2017;31. Doi: 10.1111/1365-2435.12846.
42. Pinilla L, Aguilar E, Dieguez C, Millar RP, Tena-Sempere M. Kisspeptins and reproduction: Physiological roles and regulatory mechanisms. Physiol Rev 2012;92:1235-316.
43. Wahab F, Aziz F, Irfan S, Zaman WU, Shahab M. Short-term fasting attenuates the response of the HPG axis to kisspeptin challenge in the adult male rhesus monkey (*Macaca mulatta*). Life Sci 2008;83:633-7.
44. Mechaly AS, Viñas J, Piferrer F. Gene structure analysis of kisspeptin-2 (Kiss2) in the senegalese sole (*Solea senegalensis*): Characterization of two splice variants of kiss2, and novel evidence for metabolic regulation of kisspeptin signaling in non-mammalian species. Mol Cell Endocrinol 2011;339:14-24.
45. Mazón MJ, Gómez A, Yilmaz O, Carrillo M, Zanuy S. Administration of follicle-stimulating hormone *in vivo* triggers testicular recrudescence of juvenile European sea bass (*Dicentrarchus labrax*). Biol Reprod 2014;90:1-10.
46. Rocha A, Zanuy S, Carrillo M, Gómez A. Seasonal changes in gonadal expression of gonadotropin receptors, steroidogenic acute regulatory protein and steroidogenic enzymes in the European sea bass. Gen Comp Endocrinol 2009;162:265-75.
47. Servili A, Herrera-Pérez P, Del Carmen Rendón M, Muñoz-Cueto JA. Melatonin inhibits gnRH-1, gnRH-3 and gnRH receptor expression in the brain of the European sea bass, *Dicentrarchus labrax*. Int J Mol Sci 2013;14:7603-16.
48. Herrera-Pérez P, Del Carmen Rendón M, Besseau L, Sauzet S, Falcón J, Muñoz-Cueto JA, *et al.* Melatonin receptors in the brain of the European sea bass: An *in situ* hybridization and autoradiographic study. J Comp Neurol 2010;518:3495-511.
49. González-Martínez D, Madigou T, Mañanos E, Cerdá-Reverter JM, Zanuy S, Kah O, *et al.* Cloning and expression of gonadotropin-releasing hormone receptor in the brain and pituitary of the European sea bass: An *in situ* hybridization study. Biol Reprod 2004;70:1380-91.
50. Chai K, Liu X, Zhang Y, Lin H. Day-night and reproductive cycle profiles of melatonin receptor, kiss, and gnrh expression in orange-spotted grouper (*Epinephelus coioides*). Mol Reprod Dev 2013;80:535-48.
51. Cowan M, Paullada-Salmerón JA, López-Olmeda JF, Sánchez-Vázquez FJ, Muñoz-Cueto JA. Effects of pinealectomy on the neuroendocrine reproductive system and locomotor activity in male European sea bass, *Dicentrarchus labrax*. Comp Biochem Physiol A Mol Integr Physiol 2017;207:1-2.