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A Review on Melatonin and its Prospects in Fish Aquaculture

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Review Article

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ABSTRACT

Current research and data available suggest pineal organ is the mediator that converts the information of photoperiod into melatonin. The source of melatonin is not only pineal gland but gastro-intestinal-tract (GIT) also produces a substantial amount of melatonin. The detection of melatonin-synthesizing enzymes, N-acetyltransferase and hydroxyindole-O-methyltransferase in the GIT confirmed extra-pineal melatonin synthesisthat the pineal and gut melatonins are two different systems set to perform different physiological processes. The degradation of melatonin in liver occurs only when it reaches certain threshold level. Melatonin regulates the physiological process of growth, food intake, stress and immune system and reproduction as a result of specific behavioural rhythms. Not much knowledge has been gathered on the role of melatonin in relation to physiology in fish.

Fisheries and aquaculture as the fastest protein manufacturing industry has an important role to play according to FAO [1] in meeting the world's greatest challenge of feeding a population of 9.6 billion by 2050. In recent trend of aquaculture, the surge for increase production has been second to none. Globally, understanding the physiology of fish to enhance its production is prima facia. Bromage et al. [2] advocated that reproduction in fish is known to be seasonal. India is a country with distinct seasonal variation. The molecule that sets the rhythm of the individual with the seasonal timing for reproduction is consideration to act through the hypothalamus-pituitary-gonadal axis [3,4]. The reproductive cycle is under endocrine control by hormones from the hypothalamus and other glands like the pituitary and gonads [5]. Pineal organ is the mediator that converts the information of photoperiod into melatonin [6,7]. Melatonin as a hormone is linked to many physiological functions of an organism. However, not much information has been gathered on the role of melatonin in relation to basic physiological functions in fish so as to improve our understanding of how it acts as a factor in the regulation of physiological functions such as growth, metamorphosis, reproduction, stress and disease resistance. The current review summarizes our knowledge on the role of melatonin with more emphasis on the effect of exogenous administration on physiological functions of fish as a suggestion to be a prospective molecule in aquaculture industry.

LOCALIZATION OF MELATONIN BIOSYNTHESIS

The source of melatonin is not only pineal gland but retinal and gastrointestinal tract (GIT) also produces a substantial amount of melatonin. This has been detected in fish [8-12] after pinealectomy. GIT is found to be the most abundant extra-pineal source of melatonin [13]. The detection of melatonin-synthesizing enzymes, N-acetyltransferase [14] and hydroxyindole -O-methyltransferase [15] in GIT and retina confirmed extra-pineal melatonin synthesis. This was also recently confirmed by t-polymerase chain reaction [16].

PINEAL AND EXTRAPINEAL MELATONIN

The fundamental differences between pineal- and GIT-produced melatonin is that former produced melatonin acts mostly as an endocrine substance, however, the extrapineal derived melatonin not only functions as endocrine but also as autocrine, paracrine and luminal capacity [17,18]. A recent finding has revealed that the regulatory mechanism of melatonin synthesis in gut and pineal were different even in same animal species [19]. Profiles of melatonin circulation in carp [20] exhibit precise diurnal rhythms with a peak during the dark-phase and nadir during the photo-phase and primarily such rhythms are from pineal Arylalkylamine N-Acetyltransferase (AANAT) [7]. However, the analysis of AANAT-2 mRNA expression in goldfish revealed daily rythmicity in hind gut [21]. The daily AANAT-2 mRNA expression peak was found to be independent of darkness and light. However, melatonin peak during daytime has been observed in sea bass [22]. In a study on melatonin levels and AANAT density in carp Mukherjee et al. [23]

confirmed that melatonin-synthesizing system in each gut segment showed a parallel alteration irrespective of seasons and daily variations with a peak at mid day. A typical pattern of AANAT activity was observed in the retina of trout by Besseau et al. [24] where the activity of AANAT was high during light period and low at dark. The activity of deacetylase suggested that melatonin produced in retina may have local function and it is not secreted in the blood [25].

ENVIRONMENTAL INFLUENCE ON PINEAL MELATONIN

The pineal organ translates the photoperiod information into melatonin, and one of the main functions for this message is the control of reproduction [26,27]. In fish species, the pineal organ's ability of cyclic synthesis and release of melatonin is considered as a responsive mechanism to the changes in environmental light and darkness [28]. Melatonin mediates the transduction of photoperiodic information to the brain pituitary-gonad axis in gonadal maturation of precocious male masu salmon [29]. In carp species, it was observed that highest melatonin concentration was observed during post spawning phase and the lowest levels during spawning phase [30]. This was confirmed from AANAT activity peak during post-spawning phase which coincided with the peak of the melatonin concentration [31].

The influence of temperature on melatonin levels in trout [32], pike [33] and carp [34] have been observed in an *in vitro* studies of the regulation of AANAT kinetic. Bromage et al. [2] have observed that the night time melatonin level was recorded to be lower at reduced temperature and elevated level at increased temperature. Studies have found that peak activity of AANAT reflects the preferred temperature of the fish and its adaption to the environment. The preferred temperature for trout *Oncorhyncus mykiss* (12 °C), pike *Esox lucius* (20 °C), seabream *Sparus aurata* (27 °C) and zebrafish *Danio rerio* (30 °C) [29].

Numerous studies have argued that the level of melatonin in fish is related to stress. This was reported from a recent study in tilapia *Oreochromis mossambiques* that cortisol level in plama lowers melatonin synthesis in pineal organ [35]. Further, Benyassi et al. showed that expression of glucocorticoid receptors in trout pineal suggest that glucocorticoids may inhibit AANAT activity. In rainbow trout [36] a positive correlation is observed in stressed fish during dark, however, no relationship between melatonin and cortisol was recorded in unstressed fish.

INFLUENCE ON EXTRA PINEAL MELATONIN

The independence of GIT melatonin with the LL or DD phase brings to one variable i.e., the availability of food, which could possibly serve as an important cue to the daily periodicity of melatonin synthesis. Since food intake of an organism in diurnal and nocturnal species are nearly opposite in phase it is possible that GIT melatonin synthesis is correlated with feeding in various animals including fish species. An increase of GIT melatonin was related not only to food intake but also with starvation [37]. Herrero et al. [38] observed change in melatonin levels on feeding in sea bass (*Dicentrarchus labrax*). Melatonin may also be involved in the secretion of CCK since administration of melatonin resulted in the elevation of CCK in plasma in a dose-dependent manner [39]. However, till date data from appropriate experimental studies that support this hypothesis of a direct role on food availability and its correlation on GIT melatonin system in any animal species is lacking.

Localization of melatonin-binding sites in fish osmoregulatory tissues such as gills, small intestine and kidney suggested a possible relationship of melatonin and water-ion balance [40,41]. Water salinity affected melatonin content in intestine and gills in addition to plasma melatonin in European sea bass [42]. This suggested that extra pineal tissues might also be a factor contributing to an alteration in plasma melatonin levels in response to osmotic changes.

DEGRADATION OF GIT MELATONIN

GIT Melatonin is circulated via hepatic portal vein [43-45] and degraded in the liver. The degradation of melatonin in liver occurs only when it reaches certain threshold level. This threshold level of melatonin is taken to be the level of melatonin in peripheral circulation during the day. The low melatonin level of the day-time peripheral circulation it escapes liver degradation [19,46]. However, at concentrations above the threshold level, melatonin is quickly degraded and excreted via the bile [47]. It has been reported that the concentration of melatonin in the bile range between 2000-11000 μg/μl. Such concentration of melatonin exceeds GIT melatonin concentration by 10-40 times. Jose et al. [48] also observed a 10 fold value of plasma melatonin during daytime in the bile of trout. Though, the reasons for the high levels of melatonin are unclear, one possible explanation could be that high melatonin level goes to liver for degradation and returns to the intestines.

PHYSIOLOGICAL EFFECT OF EXOGENOUS MELATONIN SUPPLY

Melatonin the "hormone of darkness as Reiter [49] termed plays a key mediator role that is responsible for synchronization of many physiological processes in almost all organisms and its molecular structure is highly conserved [50]. Melatonin controls the physiological process of growth, food intake, digestion and reproduction as a result of specific behavioural rhythms [11,51,52].

REPRODUCTION

Ovarian Activity

The impact on the seasonal cycle of reproduction by melatonin has been largely investigated by means of photoperiod manipulations, pinealectomy and melatonin administration [27,53]. The foremost explicit evidence that melatonin has an effect on reproductive cycle came from an *in vitro* study of Khan and Thomas [54] in the Atlantic croaker *Micropogonias undulatus*. The effect of exogenous melatonin supply on reproduction was dose dependent in catfish *Clarias batrachus.* In the study, Singh and Lal [55] observed that administration of melatonin at 25, 50 mg/fish significantly lowered the level of 17 alpha-hydroxyprogesterone as compared to doses supplied at 100, 200 and 400 mg/fish. Further, gonadotropin secretion and ovarian activity in stinging cat fish *Hetropneustes fossilis* was significantly affected on intra peritoneal administration of melatonin (75 mg/100 gm body weight) for 20 during early prespawning phase. The treated individuals showed significant reduction in plasma GtH and estradiol-17β levels, the gonadosomatic index, frequency distribution of vitellogenic and post vitellogenic oocytes. Mondal et al. [56] reported that exogenous treatment of 100 mg/100 g body weight/day of melatonin during the preparatory, prespawning and spawning phases of an annual reproductive cycle showed accelerated oocyte growth in the preparatory phase but the pre-spawning and spawning phases of annual cycle of Indian major carp *Catla catla* was retarded.

Testicular Activity

Exogenous supply of melatonin enhances gonad maturation via pituitary-hypothalamus-gonad axis and also acts directly on the testes through Leydig cells [57]. It has been accounted that melatonin stimulates spermatogenic activity by increasing the sensitivity of Leydig cells to GTH-II by Langford et al. [58]. Further evidence of melatonin playing a significant role in the regulation of annual testicular events was reported by Bhattacharya et al. [59] in Indian major carp *Catla catla*. A study on walking catfish *Clarias macrocephalus* male broodstock feeding exogenous level (0, 50 and 250 mg/kg diet of 37% crude protein) shows that melatonin feeding treatment to male *C. macrocephalus* has significantly enhanced the maturation of testes and sperm [60].

FOOD INTAKE

The support of melatonin involvement in the regulation of food intake via appetite regulation been reported in gold fish [61]. Treatment of oral melatonin showed an inhibitory effect on feeding in European sea bass *Dicentrarchus labrax* and tench *Tinca tinca*. Workers have reported reduction in food intake [62,63] and body weight [64] on peritoneal injection of melatonin in goldfish. In zebrafish *Danio rerio*, treatment of melatonin via water at dose (100 nM and 1 μM for 10 days) showed significant reduction in food intake [65]. The results obtained further indicate that the reduction in food intake was also in conformity with change at gene level. A significant increase in gene coding for protein involved in inhibition of feeding (Leptin and MC4R). Feeding rainbow trout *Oncorhyncus mykiss* with commercial pellets supplemented with a concentration of melatonin (0, 40 mg and 200 mg/kg/ day for 10 days) showed reduction of food intake by >50% in the treated group compared to the control group under stress conditions (high stocking density), and this effect was abolished in the groups fed with dietary melatonin supplementation in rainbow trout [66].

GROWTH

The growth in fish follows seasonal pattern of varying day-length [67] and grow differently depending on the circadian time feeding [68]. In gold fish, accelerated weight gain and growth on intraperitoneal injection of melatonin was observed [69]. Melatonin implants in Atlantic salmon parr *Salmo salar* also resulted in increased weight [55]. However, contradictory result was recorded in trout [70]. Similar observation was made by Singh et al. [71] on exogenous melatonin treatment (25 μg/L for 21 days) in Nile tilapia *Oreochromis* niloticus, showed a 36.6% reduction in specific growth rate (SGR % per day) as compared to the untreated group.

ANTIOXIDANT ACTIVITY

Melatonin not only act as a highly effective antioxidant but also as a direct scavenger of free radicals [72,73]. Melatonin protects cells from DNA damage against peroxynitrite [74]. In macrophage cell line (J774A.1), melatonin was observed to reduce lipid peroxidation level and also enhance O_2 detoxification [75]. Majority of data from *in vitro* studies demonstrates that melatonin inhibits production of hydrogen peroxide [76] and O [75]. Jung et al. [77] reports on the mitigating effects of melatonin by injection on goldfish *Carassius auratus* exposed to thermal stress (30°C water temperature) showed a significant increase in expression and activity levels of the antioxidant enzymes such as superoxide dismutase (SOD) and catalase (CAT), plasma hydrogen peroxide, lipid hydroperoxide, and lysozyme. These results suggests that melatonin inhibit oxidative stress from high temperatures induce oxidative stress and reduce immune system strength, but also boosts immune system in goldfish. In carp *Catla catla* administration of melatonin acts as an antioxidant and reduces intraovarian oxidative stress during follicular growth [56]. They found that exogenous melatonin supply of 100 μg/100 g body weight/day for 2 weeks showed significant elevations of SOD, CAT, GPX, GST, GSH levels and reduction of MDA (malondialdehyde).

IMMUNE SYSTEM

Melatonin has been observed to influence in the development of thymus, spleen and bursa [78] which are primary organs of immune system. The presence of melatonin receptors (MT1 and MT2) on leukocytes [79] suggest functional role in immunity. Melatonin, *in vitro* and *in vivo* regulates the innate and adaptive immune response [80]. Radioligand binding studies on fish cells by Falcon et al. [27] led to the identification of three high affinity melatonin receptors belonging to the GPCR family: MT1, MT2 and Mel1c. Characterization and full length cloning of melatonin receptors of trout (MT1), rabbitfish (MT1 and Mel1c), seabass (MT1, MT2 and Mel1c) and pike (MT2) have been documented by Sauzet [81], receptors MT1, MT2 and Mel1c in Senegalese sole [82] and

MT1 in *Cyprinus carpio* [83]. Further, functional studies on MT2 receptor of fish revealed that it is associated with cAMP pathway [28]. Roy [84] also had advocated earlier that melatonin modulated the activity of spleen phagocytes via a membrane receptor linked to cAMP-PKA pathway in *Channa punctatus.* However, no direct evidence on expression of melatonin receptor was reported.

Kepka [83] demonstrated the direct responsiveness to melatonin stimulation on leucocytes of common carp *Cyprinus carpio. In vitro* and *in vivo* administration of melatonin (2 mg/ml melatonin @ 1 ml/20 g body weight) in common carp *Cyprinus carpio* (60-70 g) induced decreased respiratory burst in inflamed leukocyte, decreased gene expression of CXC – chemokine (*in vitro*) and reduced number of neutrophils *in vivo* during zymosan induced peritonitis. The most significant result obtain by them was that the random migration of leukocytes was reduced in a dose dependent manner and melatonin inhibited apoptosis of leukocytes (*in vitro*). The results demonstrated that in carp, melatonin performs pleiotropic functions and that extra-pineal is important in maintaining pro- and anti-inflammatory balance during infection [85].

MELATONIN IN FISH AQUACULTURE

Photoperiod Manipulation

The periodical change in photoperiodic conditions perceived by photo sensory organs is the first step in initiating reproductive activity in fish. Melatonin secretion by the pineal of fish can be directly entrained by photoperiod, but the relationship of melatonin rhythm to photoperiodism in fish is unclear There has been reported that melatonin levels are strongly correlated with photoperiod manipulation in salmonids [2] resulting in alteration of spawning time. Concurrently, Amano [86] observed melatonin to be one of the factors that mediated the photoperiodic signals in the control of gonadal development in Masu salmon *Oncorhynchus masou*. These changes in relation to photoperiod are therefore suggested to be transduced by the melatonin rhythms that transfer this information to the brain-pituitary-gonadal axis.

Manipulation of photoperiod to delay or advance sexual maturation and spawning is now a common practice for commercially important species. Several works have been reported in many fish species. Carrillo [87] spawned rainbow trout *Oncorhynchus mykiss* in 6 months by exposure to long photoperiods (18L: 6D). In red drum Sciaenops ocellatus year round spawning could be achieved in constant photoperiod 12 L:12 D. and cycling temperatures [88]. Within a uniform compressed photothermal cycle it has been observed that barbel *Barbus barbus* matured in 6 to 7 months [89] and orange mouth corvina *Cynoscion xanthalus* matured in 8 months [90].

In commercially cultured teleost, the photoperiod of the broodstock is manipulated to achieve year-round production of gametes in sea bream *Sparus aurata* [91], sea bass *Dicentrarchus labrax* [92], sole *Solea solea* [93], rainbow trout *Oncorhynchus mykiss* [94-96], Atlantic halibut *Hippoglossus hippoglossus* [97], striped bass *Morone saxatilis* [98], turbot *Scophthalmus maximus* [99], and Atlantic salmon *Salmo salar* [100]. In salmon industry light is also used to manipulate the timing of smoltification by exposure to short day photoperiod pattern of winter during summer [101].

CONCLUSIONS

In so far, current research and data available suggest that the pineal and extrapineal melatonin are two different systems set to perform different physiological processes. The existence of multiple sites in the body where melatonin is synthesized may reflect an adaptive mechanism throughout the evolution. The chronobiotic system maintains physiological functions and uses melatonin as the main endogenous synchronizer. Though the functional characteristics of the extra-pineal, GIT melatonin system, is not understood discretely, the importance of physiological significance can be underlined. Currently, the application of melatonin exogenously on fish and its effect on the physiology is at experimental stage. The large variability in sensitivity and response to exogenous melatonin administration observed among teleost fish suggest that species-specific regimes will have to be worked upon to initiate its use in commercial set ups to standardized and improve husbandry practices (use of light, handling, broodstock management, vaccination, etc.) in fish aquaculture. Further investigations would promote potential interest for the aquaculture industry.

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