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REVIEW ARTICLE

Biological Clock and Melatonin: A Crosstalk in the Era of Artificial Light at Night (ALAN) in Fish

Zeeshan Ahmad Khan[1], Gopinath Mondal[1], Chongtham Rajiv[1], Haobijam Sanjita Devi[1], Chongtham Rajiv[1], Thangal Yumnamcha[1], Sijagurumayum Dharmajyoti Devi[1], Rajendra Kumar Labala[2], Asamanja Chattoraj[2*]

[1]Biological Rhythm Laboratory, Animal Resources Programme, Institute of Bioresources and Sustainable Development, Department of Biotechnology, Government of India, Imphal, Manipur, India

[2]Biological Rhythm Laboratory, Department of Animal Science, Kazi Nazrul University, Paschim Bardhaman, Asansol, West Bengal, India

[*]Corresponding author: Asamanja Chattoraj, *Email: asamanja.chattoraj@knu.ac.in*

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Abstract

The time keeping machinery, generally termed as the biological clock system, works through neurohormonal mechanism to anticipate in the daily and seasonal changes. This cross talk ensures individual's sustainability by maximizing the efficiency of all the biological processes. Different organisms have their own challenges depending upon their niche. The aquatic niche offers diverse environment, with fish surviving in almost all of them. A new factor, Artificial Light at Night (ALAN) has added in the fish niche. The contemporary night-time images from satellite show a boundary of light between the sea and the land, such is the extent of artificial lighting on the seacoast. Currently, the studies on the repercussion of artificial lighting at night has been substantially increased, however, they hardly address the piscine system. ALAN can directly alter the physiology and behaviour of fish, although the response route is species and life-stage specific. In this article, we have tried to present an overview of biological clock system in various classes of organism and effect of post-translational modifications on clock system. Subsequently, melatonin biosynthesis and its interplay between clock and melatonin system in fish is presented. The effect of ALAN on the fish clock system and melatonin is critically evaluated.

Keywords: *Biological Clock, Melatonin, Circadian Rhythm, Fish*

1. Introduction

The biological rhythm of an organism is maintained by the pacemakers. These rhythm pacemakers are a cluster of excitatory neurons, their activity fluctuates with 24h cycle. These neurons are present in the retina/pineal gland/SCN (Suprachiasmatic nucleus). The rhythm pacemakers are synchronized with the external stimuli such as photoperiod or temperature called as zeitgeber. Biological rhythms are entrainable, show diurnal and seasonal variations in their vascular growth, can modulate hormonal secretions corresponding to the season to increase the competence of the process and efficacy of the molecules. Studies conducted on the unicellular organism till date suggested the existence of multiple oscillators within each cell. *G. polyedra* has two oscillators, both respond to distinct wavelength of lights. One is speculated to regulate bioluminescence while other regulates phototaxis. These oscillators are considered as predominantly "master-slave oscillators". Multiple oscillators are also observed in *N. crassa* and cyanobacteria. *S. elongatus*, has a pacemaker which has kaiA, kaiB and kaiC clock genes. They control global gene expression, and even the timing of cell division. These proteins have intrinsic capability to interact with various other proteins and perform oscillatory function. Clock system is generally present across all the invertebrate phyla. The initial studies performed by Pittendrigh were on cockroaches, Leucophae amaderae. These were some of the first experiments that showed neuronal circadian pacemaker in invertebrates. Results indicated that brain and optic lobes of cockroaches are vital for robust, functional, circadian rhythm and locomotor activity(1). Further conducted experiment has

proved that optic lobe alone can be a complete neuronal pacemaker(2). These rhythms were totally abolished when the optic lobes/ tracts were surgically ablated. Regeneration of the optic lobe and mid-brains leads to reappearance of identical rhythm whereas transplants from other individual resulted in reappearance of rhythm but totally different from their own. These experiments have proved that optic lobe is a neuronal pacemaker. Silk moth is another important model to study the neuronal pacemaker. Like cockroach, silk moths are easy to handle for partial brain and retinal surgery and transplants. In depth analysis of silk moth showed that brain contains the neuronal pacemaker, and it is light sensitive too(3). The eclosion behaviour i.e., shedding the skin of silk moth is under circadian control. The process of eclosion is light driven event. Ablations of the light sensitive brain of silkmoth abolish the free running eclosion. Surgical removal of other tissues like retina has no effect on eclosion. Chronobiologists have extensively worked on Drosophila too. The autonomous circadian time keeping mechanism in Drosophila melanogaster comprises of two interlocked transcriptional feedback loops. Tissue distribution studies have proved that all the tissues of the Drosophila express clock genes. Moreover, the expression of the clock genes is found to be rhythmic in all the tissues. In the brain of Drosophila, a cluster of 4-5 small ventral lateral neurons (sLNvs) are necessary and mandatory to drive locomotor activity. These oscillators can be divided into two major category, central oscillator, and peripheral oscillator. Ectothermic animals, such as fish, circadian entrainment plays even important role in their sustainability. There biological clock must cope up not only with day/night cycles, calibrate its physiology with several parameters like photoperiod and/or water temperature at daily basis (circadian), gravitational forces which changes amplitude of tides (circatidal), magnetic waves for fish migration (circannual) etc.(4).

2. The Clock System in Fish

Transcription and translation of clock associated genes form a molecular loop and oscillate in approx. 24h cycle. Intracellular autoregulatory transcriptional/translational feedback loops containing positive and negative transcription factors are involved in the mechanism of the endogenous circadian rhythm generation as well as maintenance(5; 6; 7). Studies have shown that the positive proteins are associated with E-box of the core DNA element and activates the transcription. Contrary to that, the negative elements suppress this activity(5; 6; 7). The positive and negative loop stabilizes themselves and this controls the rhythmic expression of the clock-controlled genes and in-turn regulates several physiological and behavioural processes(8; 9). These rhythms are also in sync with the day-night cycle *invivo*. It has been speculated that the molecular mechanism underlying functioning and regulation of the clock associated circadian rhythm in case of fish is close to that of mouse. This includes TTO loop, a "core" feedback transcription-translation loop involving CLOCK and BMAL heterodimer. This heterodimer of CLOCK: BMAL initiate the rhythmic synthesis of per and cry protein, also parallel expression of a "stabilising" feedback loop represented by Rev-Erb and Ror, which further regulate the expression of Clock and Bmal. Furthermore, the regulation of the clock associated circadian rhythm in zebrafish is more complex due to presence of multiple copies of the Clock, Bmal, Per, Cry, Rev-Erb and Ror genes(9; 10; 11) (Figure 1).

2.1 Key Biological Clock Associated Proteins and their Isoform in Zebrafish

Bmal [Brain and Muscle ARNT (Aryl-hydrocarbon Receptor Nuclear Translocator)-Like Protein]:
Three isoforms of Bmal(Bmal1a, 1b and 2, formerly identified as Bmal 1, 3 and 2, respectively) have been performed till date.
Clock (Circadian Locomotor Output Cycles Kaput):
The Clock 1a was the first clock gene to be cloned in *D. rerio*. After that, identification, and molecular characterization of three clock genes.
Cry (Cryptochrome):
Cry genes has six isoforms: Cry 1a, 1b, 2a, 2b, 3 and 4. Cry 1a, 1b, 2a and 2b.
Per (Period):
Per gene has three isoforms, Per1 has two homologs (Per 1a and 1b), Per2 and Per3 genes have one isoform each. Per isoforms exhibit different spatial expression patterns.

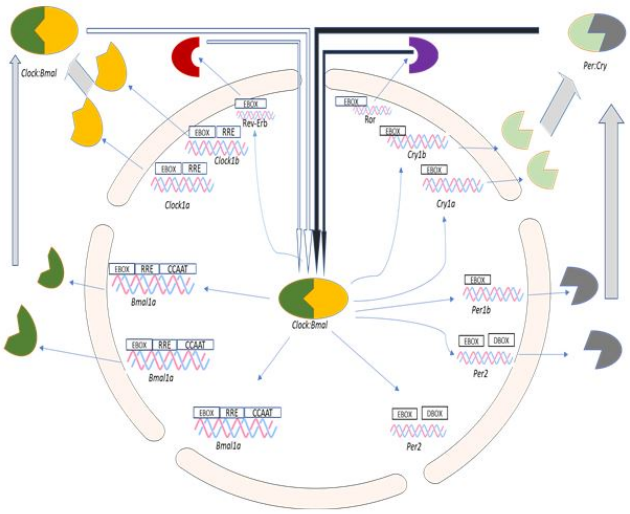

Figure 1: The functioning of clock associated genes by the transcriptional/translational feedback loops (TTFL) containing positive and negative transcription factors.

The expressivity of Clock and Bmal is dependent upon E-Box and RRE. The translated product of Clock and Bmal forms the heterodimer and further, it drives the rhythmic expression of Per and Cry which are also influenced by light (D-box and E-box). This completes the clock gene-melaton in loop in central and peripheral organs(12).

3. Post-translational Modifications

With the unravelling of several isoform of clock and explanation of TTO theory, a wide range of question have been answered, however, a lot of questions remained unanswered even with the current knowledge. The entry and export of

per proteins in the nucleus is one such unanswered query. Recently, the science of chronobiology has taken a turn towards post-transcriptional modifications. The mobility and translocation of the period and cryptochrome genes in and out of the nucleus is considered as the prime feature of the circadian control and it is performed by the phosphorylation of casein kinase (CK1 and CK2)(13; 14). These phosphorylations are speculated to be responsible for phase regulation of the circadian clock, the phasic relationship between the clock associated genes and their heterodimer formation points towards similar mechanism.The phasic relationship between the clock associated genes and formation of heterodimers in various organs of fish pointed out a similar mechanism(15; 16; 17). Despite of constant efforts from the scientists, huge number of studies are needed to understand the post-translational regulations. Precise modifications in the rhythmicity of genes may be caused by the mutations in the proteins responsible for post translational modification(18). These are non-clock, non-rhythmic gene and could be input or output related genes. Disruption in the input components of any organism causes desynchronization with the environmental cues and the manner of entrainment. On the other hand, a mutation in the output component impact several manifestations of circadian rhythmicity either in entrained or "free-running" conditions(18). Analogous reports are also available from the studies on zebrafish and cavefish(19). Nonetheless, additional studies are essential for the elaboration of the pathway.

4. Melatonin, Biosynthesis and Significance

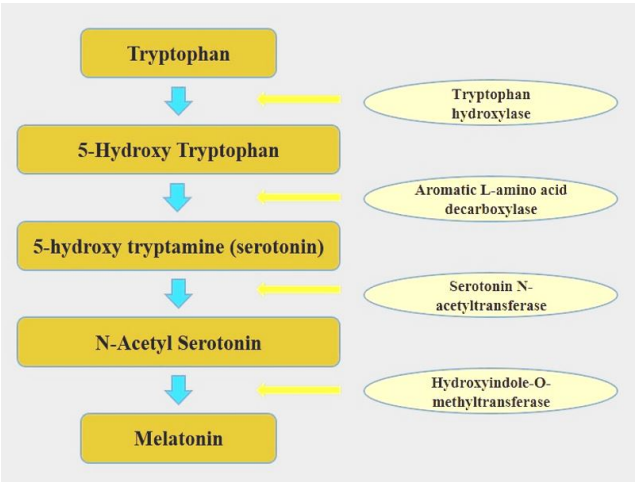

Figure 2: Schematic representation of the Melatonin biosynthesising pathway

Melatonin was first detected from the pineal gland of bovine(20). The process of melatonin biosynthesis is conserved(21; 22; 23; 24). It is a four-step process, starting from the tryptophan as the precursor. The tryptophan hydroxylase catalyses tryptophan to 5-hydroxytryptophan, which is enzymatically converted to serotonin through 5-hydroxytryptophan decarboxylase. Subsequently, arylalkylamine-N-acetyltransferase converts serotonin to N-acetyl serotonin, which is considered as the rate limiting step of the melatonin biosynthesis and it is dark dependent. Because of dark dependent activity of the rate limiting step, melatonin is biosynthesised only in darkness irrespective of the diurnal or nocturnal habit of the organism(25; 26).Methylation of N-acetyl serotonin by hydroxyindole-O-methyltransferaseis the last step of the melatonin formation. This process is highly conserved and are involved in the production of melatonin in teleost(27; 28; 29). Melatonin is multifunctional, multipotent molecule. Its function ranges from antioxidant activity, gut motility, rhythm maintenance, immune system function, in ovarian maturation etc.(30; 31; 32) The role of melatonin in ovarian development and maturation is established in mammals and lower vertebrate including fish(**?** 33; 30). Some studies have indicated the presence of melaton in synthesizing enzyme genes in reproductive organs of mammals and fish, but also in gut of fish(34; 31; 35; 36). However, the data are scarce on rhythmicity of melatonin biosynthesising enzyme genes.Two Tph isoforms have been characterized(37; 38) with different spatial expression. Tph1 isoform is exclusively present in pineal organ and peripheral tissues, while Tph2 is in brainstem raphe nuclei(39).Relationship of Tph and clock is unclear, certain investigations have claimed that Tph mRNA in amphibian retina and chick pineal showed a circadian clock regulation(40), nonetheless, nothing is known in case of fish.Among the vertebrates, the presence of two Aanat subfamilies is unique feature in the teleost(41). The Aanat1 (or AANAT1a and AANAT1b) is primarily express in the retina, while Aanat2 is expressed in the pineal gland(25; 42). The experiments performed on zebrafish (*Danio rerio*) and *Esox Lucius*(27) indicated that the clock regulation of Aanat transcripts in the melatonin biosynthesis is synchronized with central clock(43; 44), however, there is no report regarding the peripheral tissues.Hydroxyindole-O-methyltransferase, the ultimate enzyme of melatonin biosynthesis pathway is reported to be arrhythmic but might act with the Aanat in maintaining melatonin rhythm(42). Melatonin induced a significant increase in zebrafish fecundity associated with changes in the endocrine and locally produced growth factors involved in oocyte growth and maturation(45), as indicated in carp(21). Moreover, this indoleamine is supposed to give impetus to clock associated genes by influencing transcription-translation feedback loop(46).

5. Melatonin and Clock Genes

The biosynthesis of melatonin is regulated by clock genes and therefore this indole amine is the potential candidate for mediating the circadian process in animals(47).The study on zebrafish and pike(27) has clearly shown that melatonin production is influenced by a pineal clock. The same study also pointed out the regulation of Aanat transcript, the penultimate enzyme in the production of melatonin is by the circadian clock. In another study on the pineal gland of zebrafish showed that the Photoreceptor Conserved Element (PCE) and the E-box mediate the action of orthodenticle homeobox 5 (OTX5) and BMAL/CLOCK respectively to give a synergistic interaction to enhance the expression of Aanat2(48).It has also been postulated that Aanatmay have a role in the synchronization of the central clock(49). The

rhythmic correlation of the clock associated genes and melatonin synthesizing genes in the whole brain and ovary in diverse photic conditions may indicate a relationship between them. This is a clue regarding the relative contributions of the central clock and the peripheral oscillator to synchronize physiology and behaviour of the animal with the day-night cycle in vivo. In a study on seabream, it has been found that Aanat2 promoter is activated by the synergistic action of BMAL/CLOCK and OTX5(48). Further, the presence of the photoreceptor conserved element and an extended E-box were found to exist after the analysis of the promoter sequence suggests that seabream Aanat2 is a clock-controlled gene that is regulated by a conserved mechanism(48). The ex vivo studies in zebrafish Pac-2 cells revealed a mechanism of simultaneous activation of the clock and light-regulated transcription mediated by closely spaced E-box and D-box regulatory elements that are organized in proximity to the Per2 transcription start site(50). This finding also reveals a somewhat similar mechanism of light-entrainment in the central and peripheral clocks as D-box enhancers appear to serve as key elements in light-driven signalling in both centrally and cell line(50). Studies on pineal-enhanced and light-induced microRNAs (miR-183/96/182 cluster) also revealed their involvement in light and clock-regulated expression and to pineal function(51). Moreover, it has also been deduced that Tph and Bmal are regulated by the same transcription factor, NF-Y and this activation of Bmalthrough NF-Y is inhibited by Rev-Erb(11). This is an indication regarding the relative contributions of the central clock and the peripheral oscillator to synchronize the rhythm.

6. Regulation of Clock in Peripheral Tissues

The primary pacemakers in the zebrafish are the pineal gland and the retina which control its behaviour and physiology(52). It is notable that, till date functional equivalent to the SCN has not been described in fish system. Pineal gland and retina contain circadian oscillator, directly light sensitive and thereby drive rhythmic melatonin synthesis. Both central and peripheral clocks form the circadian system in zebrafish as in mammals(53). It has been demonstrated by organ and tissue culture explants experiments, that the peripheral circadian oscillators are in attendance and remarkably light sensitive throughout the organs and tissues(52; 54; 55). Moreover, embryonic cultured lines of zebrafish also displayed an autonomous intrinsic mechanism of the clock as well as light responsiveness(56; 54). The maximum feature of the clock system of zebrafish is recapitulated by Z3 cell line, which found to be the instrumental for the pathway study of the clock mechanism and light transduction(56). Duplication of clock associated genes of zebrafish was found after the characterization of molecular components. Three homologs of Clock genes(56), three Bmal(57), six Cry genes(57) and four Per(56) have been reported. The autonomous clock of the cell is driven by the formation of CLOCK:BMAL heterodimers, the central transcriptional potential. Clock and Bmal in zebrafish portray a rhythmic oscillation in their expression. These genes expressed in most tissues but with a differential peak. Moreover, the variation in the expression was also observed between the tissues/organs(57; 58). This indicates that the correct composition of CLOCK:BMAL heterodimers changes between the tissues and during the time of the day. It has been found that at the carboxy-terminal transcription activation domains of two Bmal genes are most divergent.Thus, the central transcription complex of the circadian oscillator is controlling its transcriptional potential and allowing the proper response to general and tissue-specific entraining stimuli.Similarly, Per and Cry genes also differ in their expression, light inducibility and regulation(56; 57; 58). This is the indication of the molecular complexity of the zebrafish oscillator, suggesting that the various components of this clock regulation have a differential contribution for different peripheral tissues as well as in the central(57)

7. Effect of Alan on Fish Clock and Melatonin

ALAN has opened the prospects to work in the night. ALAN has changed the work structure, and now it is impossible to imagine life without night-time lighting. The ALAN was cherished,up until the 1980s and researchers believed that the primary factor of the lifestyle diseases is due to changed diet such as switch from low to high-fat content diet. However, after a substantial amount of research on rodents with different categories of fat, it has been shown that though the lipid has an critical but minor role in the lifestyle diseases and can be managed with another source of food materials(59; 60; 61). In the 1980s, first evidence about the suppression of melatonin production by exposure to bright white light during the night was published(62). Initially, bright light with an intensity of around 2500 lux was considered as the threshold of suppression of melatonin production(62). Recent studies have shown that light intensity (blue light) of even 1 lux can cause significant suppression in nocturnal melatonin production[69,70]. Additionally, circadian disruption (arrhythmical clock genes) can be caused by the low intensity of light(63; 64; 65; 66). Such low light can be generated by our daily used electronic appliances like smartphone, computer screens, tablets, etc. These have potential to cause melatonin suppression, increased alertness, restrict sleep and may lead to the commencement of several lifestyle diseases like diabetes, cancer,etc(67). The hazardous effect of ALAN is prominent in the shift workers. According to the international agency for research on cancer (IARC), shift work which cause circadian disruption is probably carcinogenic to human68. Fish are deemed as the most vital component of the aquatic system. Fish are intriguingly associated with the food web. Extinction or decline in fish species richness is a threat to the whole biological system and will have unpredictable consequences. On an average, coastal areas are three times densely populated with human than non-coastal areas(69). Therefore, coastal areas are flooded with more ALAN. A study conducted on the pond ecosystem has shown the difference in the abundance of fish in different light schedule(70). It was discovered that the number of fish was more where the light was less or absent in comparison to the presence of light. The fish physiology as well as its behaviour is synchronized by daily and seasonal rhythms. The artificial lighting at night blurs these variations, leading to a loss in the correlation of body physiology and environment(71). Recently,

it has been shown in female European perch Percafluviatilis, and in zebrafish that light can suppress the level of gonadotropin, melatonin and modulates appetite regulatory peptides(72; 73; 74). Recent studies have revealed that melatonin play a significant role in follicle maturation in zebrafish through the brain-pituitary-reproductive axis under different photic conditions(45; 74). Furthermore, fish are mostly seasonal breeder and environment regulates its periodic phenomenon of reproduction through synchronising other physiological behaviour like feeding(75). The neurohormonal regulation of synchronization of environmental stimuli and gonadal physiology is mainly controlled by an "orchestrate phenomenon". ALAN can directly influence the ovarian physiology of the fish and leads to development of irreversible thecoma(58).

8. Conclusion

In this article, we have presented a short summary of the clock mechanism and melatonin biosynthesis mechanism, with special emphasis on fish. We have also showed that both clock and melatonin can be influenced by the ALAN. Impact of ALAN on clock associated gene and melaton leads to circadian misalignment and onset of several diseases. Further studies are needed to understand how these circadian mis-alignments might influence the fish physiology, diversity, and richness of aquatic ecosystem.

Conflict of Interest The authors have no conflicts of interest to declare.

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