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Melatonin Bio-Synthesizing Machinery in Fish: A Current Knowledge with a Special Emphasis on Tropical Carp

Haobijam Sanjita Devi[1#], Chongtham Rajiv[1#], Zeeshan Ahmad Khan[1], Gopinath Mondal[1], Sijagurumayum Dharmajyoti Devi[1], Thangal Yumnamcha[1], Rupjyoti Bharali[2] and Asamanja Chattoraj[1*]

[1]*Biological Rhythm Laboratory, Animal Resources Programme, Institute of Bioresources and Sustainable Development, Takyelpat, Imphal, Manipur, India*

[2]*Department of Biotechnology, Gauhati University, Guwahati, Assam, India*

[#]*Authors Contributed Equally*

[*]**Corresponding author:** Asamanja Chattoraj, Biological Rhythm Laboratory, Animal Resources Programme, Institute of Bioresources and Sustainable Development, Department of Biotechnology, Government of India, Takyelpat, Imphal-795 001, Manipur, India, Tel: +91-385-244-6122; Fax: +91-385-244-6121; E-mail: asamanja.chattoraj@gmail.com, achattoraj.ibsd@nic.in.

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Abstract

Melatonin is a chronobiotic molecule, mainly synthesized in the pineal organ in all vertebrates. Recent studies emphasize the production of this indole amine hormone in extra-pineal sources in fish as well as in other vertebrates. The present communication is aimed to put a light on the recent development on the extra-pineal sources of melatonin with special attention on the tropical carp. The importance and involvement of clock-associated genes are also taken into the consideration for understanding the integrate phenomenon of rhythm physiology. The uniqueness of the melatonin bio-synthesizing enzyme genes in fish has also been focused. The sudden changes in the environmental factors are affecting the daily and seasonal physiological activities of fish. Studies from our group on tropical carp *Catla catla* indicate the changes on the rhythmic pattern of these enzymes at their mRNA level. Moreover, results also focused to establish this tropical carp as a model for the studies on the rhythm biology.

Keywords: Melatonin; Fish; Serotonin; Biosynthesis

Introduction

Environmental factors have a profound effect on the temporal pattern of body physiology and behavior. The light-dark component is critical for the synchronization of an organism to co-ordinate their physiology in a rhythmic manner. This harmonization is mainly mediated by a chrono biotic molecule called melatonin, which is primarily produced by the pineal organ [1,2]. Melatonin is principally expressed during the dark phase [3]. The biological rhythm of this hormone is regulated by environmental photo-thermal conditions [4-6]. The level of melatonin rises after the onset of dark phase, attains peak at night and slowly attenuates before the onset of light hence it is termed as the "dark hormone" [3].

Unlike mammals and other vertebrates, melatonin production machinery in teleost has a wide range of diversification starting from two AANAT isoforms [2,7] to two photo sensory organs: pineal and retina [8] which work intricately to fine tune the body physiology and act according to the varying demands of light-dark cycle. Moreover, teleost are seasonal breeders and its reproductive phases are characterized by distinct melatonin profile [9,10]. These unique characteristics qualify fish in general and *Catla catla* in particular as the most suitable model to study the variation and possible reasons in the alteration of body physiology.

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 [11]. The production of melatonin involves four enzymatic steps and the precursor is tryptophan. In the first step tryptophan hydroxylase (TPH; EC 1.14.16.4) produces 5-hydroxytryptophan using tryptophan as substrate. Then 5-hydroxytryptophan decarboxylase (EC 4.1.1.28) acts on to form serotonin. After this, arylalkylamine-N-acetyltransferase (AANAT; EC 2.3.1.87) converts serotonin to N-acetyl serotonin, this step is dark dependent and thus it is called the rate limiting step and therefore, melatonin always produces only in darkness [11,12]. The last step involves the methylation of N-acetyl Serotonin by hydroxyindole-O-methyltransferase (HIOMT; EC 2.1.1.4.) to produce melatonin. The whole process of this biosynthesis is conserved [13,14].

The study on zebrafish and pike has clearly shown that melatonin production is influenced by a pineal clock [15]. 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 [16]. It has also been postulated that Aanat may have a role in the synchronization of the central clock [17,18].

The distinct pattern of these enzyme genes expression in central (pineal, retina and brain) and peripheral organs (gut, ovary etc.) provides a clue about the presence of central and peripheral clock machinery in fish to maintain homeostasis in dynamic environmental conditions [4,19,20].

Extra-pineal Sources of Melatonin: The pineal organ and retina are considered as the primary site for the melatonin biosynthesis, however, recently, the search for the melatonin bio-synthesising machinery in different organs has been expedited and the results were astonishing.

Melatonin bio-synthesising machinery were reported in brain and peripheral tissues like ovary, gut, kidney, liver, muscle and heart which plays an important role in proper functioning of the body [2,4,20-25]. This is paradigm shifting as it has increased the biological significance of melatonin and opened new vistas for melatonin research. The cells in these peripheral tissues are capable of synthesizing melatonin in synchronization with a pineal dependent central clock and able to function independently under physiological demand [26]. In the ovary, melatonin plays a crucial role in maintaining the ovarian function [10,20] and also induces oocytes maturation in *Catla catla* [27]. The expression pattern of melatonin bio-synthesizing enzyme genes in gut and brain were changed rhythmically and distinct from each other in natural photo-thermal conditions [4,22]. Remarkably, melatonin production in gut tissue is enormously higher than that of the pineal organ and plays a crucial role in many physiological functions [4,28]. The local melatonin production in gut tissue is independent of the pineal organ [4], indicates a possible involvement of clock associated genes, independent and/or governed by the central clock in fish gut. Further experimental evidence is required to establish this hypothesis.

Gut harbours microbiota which forms a symbiotic relation with the host and are involved in the metabolic functions of the host organism [29,30]. These microbiota demonstrate a diurnal variation and a rhythmic change in their structure [31] and recent findings also indicated a probable harmonization between gut microbiota and GIT melatonin [32,33]. A recent study on human gut microbiota revealed the possibility of host biological clock to regulate microbial rhythm [33] and disruption in circadian rhythm causes the alteration in a microbial structure which ultimately causes different kinds of diseases [34]. Study on fish in this aspect is warranted, especially in view of the sudden environmental changes involving the clock associated genes and melatonin.

Summary and Conclusion

Teleost are having the unique characteristics for the studies in chronobiology. Due to a substantial degree of physiological and anatomical variations, they occupy a wide and diverse habitat. The aquatic world is highly dynamic, which influences the evolution of circadian timing system to a wide range of selective pressures based on light, temperature and water pressure. The orientation and circadian organization of the clock system in fish indicates a complex and inter-connected mechanism of functioning. The involvement of environmental clue is essential for the rhythm organization and clock operation. The circadian oscillator located centrally receives the external clue and mediate the information to the peripheral system. Melatonin may act as a mediator between the central and peripheral systems, which is superintended by clock genes centrally [20].

The work on carp *Catla catla* indicates a seasonal and diurnal variation of four major melatonin bio-synthesizing enzyme genes in an annual cycle of a tropical carp in brain and gut. It is evident from the statistical analysis that the rhythm of transcription of all these genes is mostly insignificant in a daily basis, but an overall variation can be seen depending on the photo-thermal conditions [4]. Moreover, the expression of both isoforms of Aanat in pineal and retina also implies the significance of their origin from the same ancestral photodetector [2]. Moreover, the existence of major melatonin bio-synthesizing enzyme genes in several tissues indicated the possible importance of this indole amine for the different physiological purpose.

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