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Review article

Melatonin synthesis and clock gene regulation in the pineal organ of teleost fish compared to mammals: Similarities and differences

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ABSTRACT

The pineal organ of all vertebrates synthesizes and secretes melatonin in a rhythmic manner due to the circadian rhythm in the activity of arylalkylamine N-acetyltransferase (AANAT) – the rate-limiting enzyme in melatonin synthesis pathway. Nighttime increase in AANAT activity and melatonin synthesis depends on increased expression of *aanat* gene (a clock-controlled gene) and/or post-translation modification of AANAT protein. In mammalian and avian species, only one *aanat* gene is expressed. However, three *aanat* genes (*aanat1a, aanat1b,* and *aanat2*) are reported in fish species. While *aanat1a* and *aanat1b* genes are expressed in the fish retina, the nervous system and other peripheral tissues, *aanat2* gene is expressed exclusively in the fish pineal organ. Clock genes form molecular components of the clockwork, which regulates clock-controlled genes like *aanat* gene. All core clock genes (i.e., *clock*, *bmal1*, *per1*, *per2*, *per3*, *cry1* and *cry2*) and *aanat2* gene (a clock-controlled gene) are expressed in the pineal organ of several fish species. There is a large body of information on regulation of clock genes, *aanat* gene and melatonin synthesis in the mammalian pineal gland. However, the information available on clock genes, *aanat* genes and melatonin synthesis in photoreceptive pineal organ of teleosts is fragmentary and not well documented. Therefore, we have reviewed published information on rhythmic expression of clock genes, *aanat* genes as well as synthesis of melatonin, and their regulation by photoperiod and temperature in teleostean pineal organ as compared to mammalian pineal gland. A critical analysis of the literature suggests that in contrast to the mammalian pineal gland, the pineal organ of teleosts (except salmonids) possesses a well developed indigenous clock composed of clock genes for regulation of rhythmic expression of *aanat2* gene and melatonin synthesis. Further, the fish pineal organ also possesses essential molecular components for responding to light and temperature directly. The fish pineal organ seems to act as a potential master biological clock in most of the teleosts.

1. Introduction

The pineal gland is an unpaired neuroendocrine organ present in most of the vertebrates (Vollrath, 1981; Gupta et al., 2005; Gupta, 2016). It synthesizes and secretes a hormone called melatonin, and plays a very important role in transduction of light and dark information to the organism to synchronize a number of vital physiological and behavioral processes in accordance with consistent daily and seasonal variations in photoperiod (Borjigin et al., 2012; Falcon et al., 2007a). A well conserved physiological function of the pineal gland is to produce melatonin (an indoleamine hormone that is involved in regulation of biological rhythms) in a rhythmic manner (Klein, 2004).

The mammalian pineal gland is composed of epithelial cells called pinealocytes, which lack photopigments, are no longer photosensitive and act as pure endocrine cells, and hence termed as pineal gland. However, the pineal organ of teleosts and other sub-mammalian vertebrates is composed of true cone-like photoreceptor cells, which share structural analogies with the retinal cones and also secrete melatonin (Ekström and Meissl, 1997; Falcon, 1999; Falcon et al., 2007b; Mano and Fukada, 2007; Gupta, 2016). Thus, the fish pineal performs dual functions of a photoreceptor as well as that of an endocrine tissue, and hence it is termed as pineal organ (Vollrath, 1981; Gupta, 2016). The mammalian pineal gland acts as a neuroendocrine organ and receives light-dark information via retina-suprachiasmatic nucleus (SCN)-superior cervical ganglion (SCG) - nervi conarii adrenergic pathway (Gupta et al., 2005). The pineal organ appears as an end-vesicle connected by a slender stalk to the dorsal epithalamus in most of the vertebrates. In teleost, the end vesicle is located in a “window” below the skull through which light can easily enter (Gupta and Premabati, 2002; Ekström and Meissl, 2003; Falcon et al., 2010b; Gupta, 2016)

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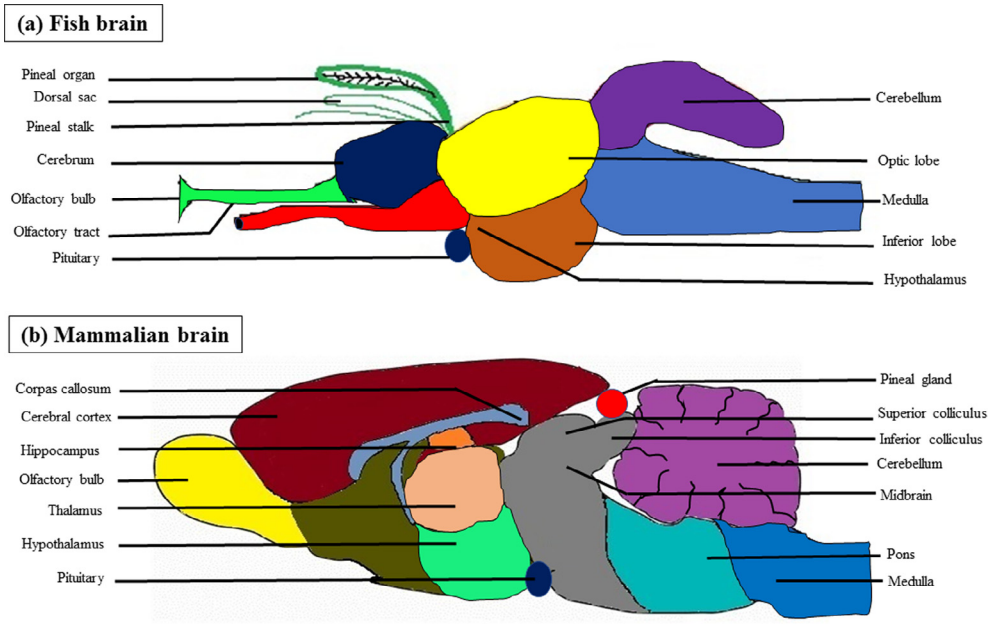

Fig. 1. Schematic diagrams depicting location of the pineal organ in (a) fish brain, and the pineal gland in (b) mammalian brain.

[Fig. 1 (a)].

The diurnal rhythm in the activity of AANAT enzyme controls the diurnal rhythm in melatonin synthesis in the pineal gland (Baler et al., 1999; Gupta et al., 2005). Melatonin production is controlled by systems that include endogenous circadian oscillators, light detectors, and melatonin synthesizing machinery. Although a rhythm in pineal melatonin production is a constant feature of vertebrate physiology, the anatomical organization of melatonin rhythm generating systems differs markedly among vertebrate classes. In mammals, generation of melatonin rhythm involves retina (photodetector), suprachiasmatic nucleus (SCN; master clock) and the pineal gland which contains all enzymes for melatonin synthesis (Gupta et al., 2005; Sinitskaya et al., 2006; Coomans et al., 2015). In lower vertebrates, photoreceptors of the pineal organ contain all the three components, i.e., photodetector, oscillator and melatonin synthesizing machinery for generation of melatonin rhythm (Gupta and Premabati, 2002; Gupta 2016). Molecular clock localized in the photoreceptive pineal organ of teleost regulates *aanat* gene expression (Iuvone et al., 2005; Gupta, 2016).

The activity of AANAT enzyme is regulated by the degree of expression of arylalkylamine N-acetyltransferase gene (*aanat* gene), which exhibits diurnal rhythm in its expression in the pineal gland of majority of mammals resulting in more than 150-fold increase in *aanat* gene expression during night time (Engel et al., 2004; Gupta et al., 2005). In the pineal gland of humans and ungulates [Fig. 1 (b)], the expression of *aanat* gene remains unchanged during day and night resulting in constantly elevated *aanat* gene enabling AANAT protein to be synthesized continuously (Spessert et al., 2006; Gupta and Spessert, 2007).

Nocturnal elevations in melatonin and AANAT mRNA levels in rodent pineal gland are controlled by the SCN via the postganglionic –adrenergic mechanism (Klein et al., 1997). At night, the SCN sends signals to release norepinephrine (NE) from the postganglionic sympathetic neurons, which activates the protein kinase A (PKA)– cAMP response element binding protein (CREB)– cAMP response element (CRE) signaling cascade via β-adrenergic receptors, and thereby activates the *aanat* gene transcription (Gupta et al., 2005). However, the roles of adrenergic mechanism as well as types/isoforms of adrenergic receptors in the regulation of *aanat* gene expression in the fish pineal organ are not well established. As in mammalian pineal, activation of β-adrenergic receptors in fish pineal organ has also been reported to increase cAMP formation leading to an increase in *aanat* gene expression via protein kinase A (PKA)–cAMP response element binding protein (CREB)–cAMP response element (CRE) signaling cascade pathway (Gupta et al., 2005). However, unlike in mammalian pineal, activation of α-adrenergic receptors inhibits the activity of AANAT activity in pike and trout (Falcon et al., 1991). Activation of both cAMP and calcium cascades is necessary to fully increase the *aanat* mRNA levels. It has been reported that time of day-dependent *aanat* gene expression is controlled by mechanisms located downstream from the PKA, where activation may be controlled by calcium and calmodulin kinase II (CaMKII) (Chansard et al., 2005). Ca^{2+} influx is required for the α1-adrenergic potentiation of the β-adrenergic stimulation of cAMP and cGMP (Gupta et al., 2005).

Rhythmic stimulatory and inhibitory outputs generated by SCN (the master oscillator) control the rhythm in melatonin production in the pineal gland of mammals (Perreau-Lenz et al., 2003) [Fig. 2 (b)]. Genetic mechanisms involving clock genes coding for transcription factors working in negative and positive loops have been reported to drive indigenous circadian oscillation in SCN (Simonneaux et al., 2004). Several clock genes and their protein products form an intricate autoregulatory transcription-translation feedback loops thereby regulating the transcription of clock-controlled genes like *aanat* gene. The protein products of *clock* and *bmal1* genes, CLOCK (circadian locomotor output cycles kaput) and BMAL1 (Brain and muscle arylhydrocarbon receptor nuclear translocator-like protein1) act as positive regulators, while the protein products of three *period* (*per1*, *per2 and per3*) genes and two *cryptochrome* (*cry1* and *cry2*) genes (i.e., PER1, PER2, PER3, CRY1 and CRY2) function as negative regulators of the autoregulated loop of transcription of core clock genes. The autoregulatory feedback loop starts with the hetero-dimerization of transcription factors CLOCK and BMAL1, translocation of the dimer from the cytosol to the nucleus, and its binding to the E-box *cis*-regulatory enhancer sequences in the promoters of *per* and *cry* genes, thereby enhancing the transcription of the genes encoding the negative components PER1, PER2, and PER3, CRY1 and CRY2 (Husse et al., 2015). This leads to increase in PER1, PER2 and PER3 levels in the cytoplasm with each protein reaching its peak level at different circadian time points (Jung et al., 2003). PER1 and PER2 are important for the clockwork but PER3 has been reported to be dispensable for circadian clock regulation (Zheng et al., 2001). PER (PER1, PER2 and PER3) and CRY (CRY1 and CRY2) proteins, when

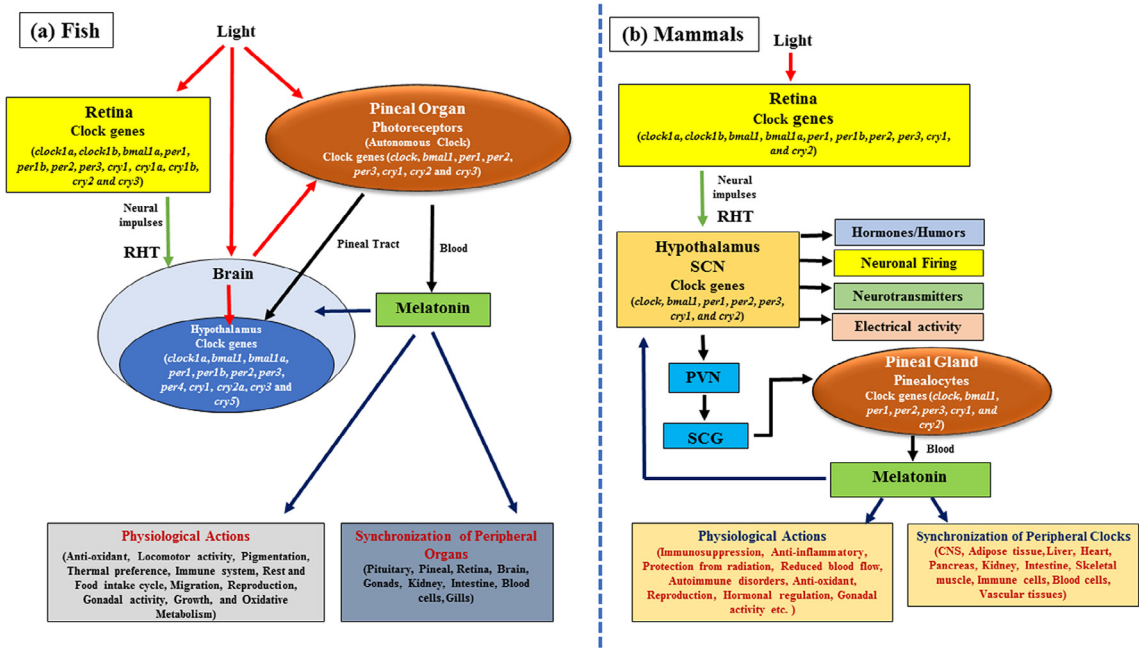

Fig. 2. Schematic representation of photic regulation of melatonin synthesis and clock genes in (a) fish and (b) mammals. PVN = paraventricular nucleus, RHT = retino-hypothalamic tract; SCG = superior cervical ganglion, and SCN = suprachiasmatic nucleus.

accumulated in adequate amount, heterodimerize with each other, get translocated to the nucleus and inhibit the transcription of *per1, per2*, *per3*, *cry1* and *cry2* genes by blocking transcriptional activity of CLOCK/BMAL complex (Tosini et al., 2008). As a result of blocked transcription of *per* and *cry* genes, the levels of PER (PER1, PER2, and PER3) and CRY (CRY1 and CRY2) proteins in the cytoplasm gets depleted during later part of the day. Due to decline in PER and CRY proteins, inhibition of transcription of *clock* and *bmal1* genes by the negative regulators (heterodimers of PER and CRY) becomes inefficient and once again there is stimulation of transcription of *per* and *cry* genes by the positive regulators (heterodimers of CLOCK and BMAL1) (Barnes et al., 2003).

There is a large body of information on the clock system and regulation of melatonin synthesis in the mammalian pineal gland. However, there is paucity of information on the circadian rhythms of expression of clock genes and clock-controlled genes, and their regulation by photoperiod and temperature in the pineal organ of teleosts. Therefore, we thought it worthwhile to review scattered information on rhythmic synthesis of melatonin, expressions of clock genes and their regulation by photoperiod and temperature in the fish pineal organ. It seems that, in contrast to the mammalian pineal gland, the pineal organ of teleosts (except salmonids) possesses a well developed indigenous oscillator composed of clock genes and their protein products, which regulates rhythmic expression of the clock-controlled *aanat2* gene and melatonin synthesis. Further, the clockwork of the pineal organ is directly influenced by photoperiod and temperature.

2. *Aanat* genes and AANAT activity in the pineal

AANAT enzyme exhibits daily rhythm in its activity with higher enzyme activity during night-time and lowest activity during day-time in all vertebrates (Ben-Moshe et al., 2014; Falcon et al., 2010b; Gupta et al., 2005; Vuilleumier et al., 2007). In general, pineal AANAT protein content/activity depends on the transcription of *aanat* gene (Gupta et al., 2005). Diurnal rhythm in *aanat* gene expression has been observed in the pineal organ of most of the vertebrates with higher pineal *aanat* gene expression levels during the night/dark phase and low during the day/light phase (Fukuhara and Tosini, 2008; Lee et al., 2009; Ho and Chik, 2010; Mcstay et al., 2014). The rhythmic expression of *aanat* gene seems to be conserved in all vertebrates. *Aanat* mRNA levels remain constant during the 24 h period with no marked diurnal fluctuation in pineal *aanat* mRNA contents in the pineal gland of primates and ungulates (Gupta et al., 2005). However, AANAT protein and its activity show dramatic diurnal rhythmicity consistent with those observed in pineal organs of another vertebrate (Spessert et al., 2006). In the pineal gland of primates and ungulates, *aanat* gene is transcribed, and AANAT protein is synthesized at a constant rate irrespective of day/light phase and night/dark phase. However, post-translational modification of AANAT protein results in diurnal rhythm in AANAT protein/activity. In primates and ungulates, during night/dark phase the newly synthesized pineal AANAT becomes phosphorylated to pAANAT by adrenergic mechanism-dependent cAMP-activated cAMP-dependent protein kinase (PKA) and forms a complex with a regulatory protein called 14-3-3 protein (Schomerus and Korf, 2005). As a result, the proteasomal enzymes are unable to degrade pAANAT complexed with 14-3-3 protein resulting in increased AANAT protein content and activity during the night, and hence increased the rate of melatonin synthesis during the night (Gupta et al., 2005). During day time, there is no phosphorylation of AANAT to pAANAT and no formation of AANAT/14-3-3 complex, and hence no protection of AANAT against the proteolytic actions of proteasomal enzymes. This leads to increased degradation of AANAT protein during the day time resulting in decreased AANAT protein, AANAT activity and the rate of melatonin synthesis (Gupta and Spessert, 2007; Maronde and Stehle, 2007). Thus, post-transcriptional modification of AANAT seems to play an important role in regulation of AANAT activity in primates and ungulates, whereas in other groups of mammals the diurnal rhythm in *aanat* gene expression seems to play a dominant role in shaping the diurnal rhythms of AANAT activity and melatonin synthesis (Coon et al., 1999).

Apart from cAMP response element (CRE), AANAT promoter contains elements that bind orthodenticle and cone/rod homeobox and the E-boxes which help in regulating its transcription (Ho and Chik, 2010; Rohde et al., 2014). E-box has been reported to be involved in regulation of *aanat* gene expression in rat pineal gland (Humphries et al., 2007). Under light-dark (LD) cycles, *aanat* gene expression in the pineal gland of rat show diurnal rhythm and as such show more than 100 fold increase in *aanat* mRNA level within first few hours just after the onset of darkness (Roseboom et al., 1996). However, in primates and ungulates, marked night/day difference in *aanat* mRNA as found in other

vertebrates is absent even though transcript level is high thereby enabling AANAT protein to be synthesized continuously (Schomerus et al., 2000). In the avian pineal organ, a rhythm in melatonin and AANAT activity parallel the rhythm in *aanat* mRNA (Bernard et al., 1997). Circadian oscillator present in the pineal gland seems to share a close link with the *aanat* gene as *aanat* mRNA shows rhythm under constant lighting conditions (Chong et al., 2000). The robust rhythm of *aanat* mRNA has also been reported in pineal organ of birds (Toller et al., 2006). It is important to mention that only one *aanat* gene is reported in the pineal gland of mammals and birds (Gupta et al., 2005). It is noteworthy that in frogs, only *aanat1* is reportedly expressed in photoreceptor cells of the retina and pineal organ as well as in diencephalic areas including cells bordering the third ventricle and cell bodies in the suprachiasmatic area (Isorna et al., 2006). However, three *aanat* genes (*aanat1a*, *aanat1b*, and *aanat2*) are expressed in teleosts (Singh et al., 2017). *Aanat1a* and *aanat1b* genes are expressed in the retina, the nervous system and peripheral tissues for regulating synthesis of melatonin, which acts as a paracrine hormone and protects these tissues from oxidative damage (López-Olmeda et al., 2006; Zilberman-Peled et al., 2006; Shin et al., 2011; Paulin et al., 2015). *Aanat2* gene is expressed exclusively in the fish pineal organ where it regulates melatonin synthesis that is released into the blood (López-Patiño et al., 2011; Paulin et al., 2015; Singh et al., 2017). *Aanat2* gene is an important clock-controlled gene in the pineal organ of teleosts (Singh et al., 2017). Rhythmic expression of *aanat2* gene in the pineal organ strongly suggests that it is an important oscillator in teleosts (Singh et al., 2017).

3. Diurnal rhythm of melatonin

Rhythmic secretion of melatonin is a highly conserved characteristic of vertebrates, which is regulated by an internal clock (oscillator) and entrained by light-dark cycle. Melatonin is produced primarily during the night/dark phase and inhibited during day/light phase of the light-dark cycle resulting in a diurnal rhythm of melatonin (Claustrat and Leston, 2015). The pineal gland, due to the diurnal rhythm of melatonin under light-dark cycle, gives information about the time of the day and night to photo-insensitive tissues/organs and acts as a peripheral clock (Klein, 2006; Falcon et al., 2009).

The diurnal rhythm of AANAT activity and melatonin synthesis in the pineal gland of vertebrates is controlled by the circadian clock and synchronized by environmental photic and thermal signals (Gupta, 2016). In mammals, the oscillations of AANAT activity and melatonin production are driven by the SCN located in the hypothalamus, which functions as the master biological clock and synchronizes peripheral oscillators/clocks in a large number of cells/tissues/organs (Dibner et al., 2010; Pfeffer et al., 2018). In mammals, photic information received by retina are conveyed via the retino-hypothalamic tract to SCN (Touitou, 2016), which then transmits its rhythmic information through multisynaptic pathways from SCN through brain stem, spinal cord, superior cervical ganglia, and postganglionic sympathetic nerve fibers (nervi conarii) to the pineal gland to drive diurnal rhythm of AANAT activity and melatonin in the pineal gland (Gupta et al., 2005) [Fig. 2 (b)]. In mammals, daily melatonin rhythm is essential for transducing day-length information into seasonal physiological responses (Johnston and Skene, 2015). The pineal organ of teleosts is composed of photoreceptor cells which possess autonomous oscillator, photopigment and melatonin synthesizing machinery/enzymes (Gupta and Premabati, 2002) [Fig. 2 (a)]. Thus, the teleostean pineal organ contains all the components required for melatonin rhythm generation within individual photoreceptor cells (Bolliet et al., 1996; Falcon et al., 2010a; Gupta, 2016). Besides photoreceptors of the retina and pineal organ, there are deep brain photoreceptors, which play an important role in the regulation of the diurnal rhythm and seasonal reproduction in teleosts (Fernandes et al., 2013; Hang et al., 2016; Horstick et al., 2017). Rhythmic melatonin secretion has been described in the pineal organ of different teleostean species such as white sucker, goldfish, pike, trout, lamprey, zebrafish, seabream, catfish, and seabass (Gupta and Premabati, 2002; Iigo et al., 2007a,b; Migaud et al., 2007; Lima-Cabello et al., 2014; Gupta, 2016).

4. Photoperiodic and thermal regulation of *aanat2* gene and melatonin synthesis

Under natural environment, there are significant monthly and seasonal changes in photoperiod and temperature over the annual time scale. In general, increase and decrease in daylength are associated with increase and decrease in temperature. However, under various climatic and geographical conditions, temperature undergoes significant variations irrespective of daylength. As a result, seasonal changes in daylength are predictable, while changes in temperature are unpredictable. Homeotherms (mammals and birds) use highly predictive daylength as a dependable environmental cue to synchronize their annual events (Lu et al., 2010; Chen et al., 2017). However, the ambient temperature affects the physiology and behaviors of teleosts significantly as these animals are unable to maintain their body temperature. Studies on different species of teleosts have shown that there is an optimal temperature where melatonin production and AANAT activity is highest (Rensing and Ruoff, 2002; Cazamea-Catalan et al., 2013).

There are few reports on effects of photoperiods on the diurnal/diurnal rhythm of *aanat2* gene expression in the fish gland organ. Diurnal rhythm in *aanat2* gene expression has been reported in the pike pineal organ under 12L-12D, LL and DD conditions as well as in the zebrafish pineal organ cultured *in vitro* under 12L-12D and LL conditions, but not in the trout pineal organ (Begay et al., 1998). In gilthead sea bream (*Sparus aurata*), quantification of *aanat2* mRNA levels in the pineal organ revealed rhythmic expression pattern under 12L-12D conditions (Zilberman-Peled et al., 2007). In the cultured pineal organ of the gilthead sea bream, the daily rhythmic expression pattern of *aanat2* mRNA was maintained under constant illumination, but the amplitude of the rhythm was reduced (Begay et al., 1998). Higher *aanat2* mRNA abundance has been reported in the pineal organ of a flatfish (*Solea senegalensis*) at mid-dark than at mid-light phase (Isorna et al., 2009). Recently it has been reported that the diurnal rhythm in *aanat2* expression was observed in the pineal organ of *Clarias gariepinus* under 12L-12D, 16L-8D, 8L-16D, LL and DD under *in vivo* conditions as well as *in vitro* under 12L-12D, LL and DD conditions (Singh et al., 2017).

Photoreceptors present in the fish pineal organ detect light providing information on light intensity, spectral content, and duration of day length (Falcon et al., 2010b). In addition to the excitatory neurotransmitter, the photoreceptors of both pineal organ and retina produce melatonin at night, following cell depolarization (Falcon et al., 2007b). Photoreceptor cells of the pineal organ perceive light stimuli causing hyperpolarization of the cells that results in the inhibition of an excitatory neurotransmitter. At the onset of dark phase, photoreceptor cells become depolarized releasing excitatory neurotransmitter which reaches the brain through the ganglion cells (Falcon et al., 2010b). Depolarization of photoreceptor cells allows accumulation of cAMP and calcium (Ca^{2+}) entry (through voltage-gated Ca^{2+} channels) where both allow phosphorylation of the AANAT2 protein are thereby contributing to increased AANAT2 amount and activity (Falcon, 1999). When exposed to light this process got reversed, where light stimuli induce photoreceptor hyperpolarization, dephosphorylation and degradation of AANAT2 through proteasomal proteolysis which results in the decrease of melatonin production (Falcón et al., 2001). The circadian/diurnal rhythms of *aanat* gene expression and melatonin production have been reported to be driven by an endogenous clockwork present in light-sensitive pineal organ of all teleosts except salmonids [e.g., rainbow trout (*Oncorhynchus mykiss*), masu salmon (*Oncorhynchus masou*), sockeye salmon (*Oncorhynchus nerka*), common whitefish (*Coregonus lavaretus*), grayling (*Thymallus thymallus*), Japanese huchen (*Hucho perryi*), Japanese char (*Salvelius leucomaenis pluvius*), brook trout

(*Salvelius fontinalis*), brown trout (*Salmo trutta*) and chum salmon (*Oncorhynchus keta*)] (Begay et al., 1998; Masuda et al., 2003; Iigo et al., 2007a,b; Singh et al., 2017). The absence of *aanat* transcripts rhythm in the pineal organ of salmonids results due to the lack of a functional clock, and thus light appears to control melatonin production directly probably at a post-transcriptional level (Coon et al., 1998). However, there are reports on the presence of an endogenous clock in the pineal organ which regulates diurnal changes in AANAT2 activity and *aanat2* gene of pike and *Clarias gariepinus* (Coon et al., 1999; Falcon, 1999; Singh et al., 2017). Light stimuli drive changes in *aanat2* mRNA resulting in to changes in AANAT2 activity, and probably act through two pathways. Photoperiod can entrain and reset the endogenous circadian clock thereby generating the rhythm in *aanat2* mRNA and AANAT activity, and hence melatonin synthesis (Falcon et al., 2010b). Light may also act directly on the pineal organ independently of the clock to suppress AANAT2 activity as seen in low day level of pike AANAT activity, and where light has been reported to suppress AANAT activity and melatonin synthesis at night (Falcon, 1999; Masuda et al., 2003). The importance of this mechanism becomes more obvious in salmonids lacking a clock where light appears to be the dominant regulatory mechanism controlling day/night changes in AANAT activity and melatonin production (Falcon, 1999; Masuda et al., 2003; Iigo et al., 2007a,b). It has been speculated that the pineal organ of ancestral protacanthopterygians harbor the circadian clock, but ancestral salmonids lost the circadian regulation of melatonin production in the pineal organ during evolution after the divergence from Osmeriformes/Esociformes (Iigo et al., 2007a). Though mechanism controlling *aanat* gene expression and AANAT activity may vary among different species, cAMP appears to be the principal second messenger controlling AANAT activity in most vertebrates (Gupta et al., 2005; Karolczak et al., 2005; Gupta, 2016). In pineal organ of trout, Ca^{2+} ions seem to play a regulatory role in controlling melatonin biosynthesis as blocking of voltage-gated ion channels lead to inhibition of melatonin biosynthesis during the dark phase (Kroeber et al., 2000).

In the pineal organ of pike maintained under 12L-12D, notable changes in *aanat2* transcripts were observed with the amplitude of the retinal *aanat1* rhythm greater than 20-fold and that of pineal *aanat2* gene greater than 8-fold (Coon et al., 1999). Pineal *aanat* mRNA levels from intact animals kept under 11L-13D were found to be 8-fold higher at 2400 h than at 1200 h and this rhythm for *aanat* transcript persisted under constant light (LL) or constant darkness (DD) although amplitude was 4 and 2.5 fold respectively (Begay et al., 1998). Moreover, *in vitro* culture of zebrafish pineal organ under LD conditions after three days showed a rhythm in *aanat* mRNA levels with the transcript 5-fold more abundant at midnight than at midday. Similarly, a rhythm was also detected *in vitro* under LL in zebrafish pineal organ (Begay et al., 1998). However, it has been reported that pineal organ of trout did not exhibit marked difference in *aanat* transcript levels under any lighting conditions (LD, LL, and DD) both under *in vivo* and *in vitro* conditions (Begay et al., 1998). Temperature has also been reported to influence AANAT activity and melatonin synthesis in the pineal organ of several fish species (Table 1).

5. Clock genes in teleosts

Attempts have been made to investigate the role of core clock genes (*clock*, *bmal1*, *per,* and *cry*) in the clockwork of teleosts. Clock genes have been studied in the brain and pineal organ of zebrafish (Moore and Whitmore, 2014). So far three *clock*, three *bmal*, four *per*, and seven *cry* genes have been reported in the zebrafish (Wang, 2008, 2009; Haug et al., 2015; Zhou et al., 2016). So far only *clock1a*, *bmal1a, bmal2*, *per1a, per2*, *per3*, *cry1a,* and *cry3* have been expressed in the pineal organ of the zebrafish (Cermakian et al., 2000; Ishikawa et al., 2002; Pierce et al., 2008; Vatine et al., 2009; Ben-Moshe et al., 2014). Zebrafish is one of the major teleost fish models where the molecular clock has been well documented (Vatine et al., 2011). Expression of core clock genes like *clock* (Huang et al., 2010a,b; Mcstay et al., 2014), *bmal1* (Hur et al., 2012), *bmal1* and *bmal2* (Cermakian et al., 2000), *per1* (Huang et al., 2010a,b; Hur et al., 2012), *per2* (Ziv et al., 2005; Ziv and Gothilf, 2006; Sugama et al., 2008; Hur et al., 2012; Ben-Moshe et al., 2014; Ikegami et al., 2014; Mcstay et al., 2014; Mogi et al., 2015), *per3* (Pierce et al., 2008), *cry1* (Hur et al., 2012; Ikegami et al., 2014), *cry2* (Huang et al., 2010a,b; Mcstay et al., 2014) and *cry3* (Ikegami et al., 2014) has been reported in the fish pineal organ. However, each of these studies investigated the expression of only few clock genes, but not all the core clock genes to establish a fully functional pineal clock as reported in mammalian SCN. Isorna et al. (2017) have described the correlation between the circadian and endocrine system in teleost endogenous oscillator entrained by the light-dark cycle, and proposed a new model for non-photic (endocrine) entrainment, highlighting the importance of the bidirectional cross-talk between the endocrine and circadian systems in fishes. Further, *rora* gene has also been reported to display a diurnal rhythm in its expression in the skeletal muscle of zebrafish (Amaral and Johnston, 2012).

There are mostly fragmentary reports on effect of photoperiods on expression of core clock genes in the pineal organ of golden rabbitfish; *per* gene (Park et al., 2007), Atlantic salmon; *clock*, *per1 like* and *cry2* genes (Huang et al., 2010a,b), threespot wrasse; *bmal1*, *per1*, *per2*, and *cry1* genes (Hur et al., 2012), European seabass; *clock* and *per1* genes (Mcstay et al., 2014), goldlined spinefoot; *per2*, *cry1* and *cry3* genes (Ikegami et al., 2014) and flounder; *per2* gene (Mogi et al., 2015). Further, lunar cycle and moonlight have also been reported to influence the expression of few clock genes in the fish pineal organ (Sugama et al., 2008; Ikegami et al., 2014). The role of photoperiod, temperature, food and tidal cycles has been reported to have an impact on the fish circadian system (López-Olmeda, 2017). Though pineal organ of teleost seems to act as both photo and thermal transducer (Singh et al., 2017), there are only a few reports on the effect of temperature on expression of clock genes in different tissues of fish species. Temperature has been reported to influence the expression rhythm of clock genes in the whole preparation of larvae of zebrafish (Kaneko and Cahill, 2005; Lahiri et al., 2005) and slow and fast muscle fibers of Chinese perch (Wu et al., 2016).

6. Conclusions

A critical review of the literature reveals that while the rhythmic synthesis of melatonin in the mammalian pineal gland involves photoreception by retina and clock function of SCN which possesses all core clock genes and enable it to function as a master clock. However, the primitive hypothalamus/SCN of any fish species does not seem to express all the core clock genes, and hence can not act as a master clock in teleosts. Unlike the hypothalamic SCN, photoreceptors of the fish pineal organ possess photo detector system, oscillator and all enzymes for melatonin synthesis. There are several reports on the rhythmic expression of core clock genes and clock-controlled genes (e.g., *aanat2* gene) in the pineal organ fish. It seems that the pineal organ of most of the fish species (except salmonids) possesses a well developed indigenous clockwork composed of clock genes and their protein products, which regulates rhythmic expression of the clock-controlled *aanat2* gene and melatonin synthesis irrespective of photoperiod, temperature and seasons. Rhythmic expression of the core clock genes and the clock-controlled *aanat2* gene under *in vitro* conditions seems to suggest that the fish pineal organ is a potential master clock which possesses a well-developed central clock as compared to the fish SCN. The existence of the diurnal rhythm of expression of all core clock genes and *aanat2* gene irrespective of photoperiod, temperature and seasons strongly suggests that the photoreceptive fish pineal organ has evolved indigenous clockwork and acts as the master biological clock for precise control over the diurnal rhythm of expression of the *aanat2* gene and melatonin. Highly advanced migratory salmonids experience extreme long and short photoperiod. Therefore, the lack of circadian regulation

Table 1
Effects of temperature on *aanat2* gene expression, AANAT activity and melatonin secretion in the retina and the pineal organ of fish species.

Fish Species	Experimental condition(s)	Observed effects	Reference
Goldfish (*Carassius auratus*) (Pineal organ culture)	25 °C under 12L-12D and reversed 12D-12L	Rhythmic melatonin secretion with high amount was reported during dark phase and low amount during the light phase	Iigo et al. (1991)
Rainbow trout (*Salmo gairdneri*) (Pineal organ)	12L-12D 9 °C	The amplitude of melatonin peak was found to increase with increasing temperature and melatonin secretion with a higher during dark phase	Max and Menaker (1992)
White sucker (*Catostomus commersoni*)) (Pineal organ)	12L-12D 10 °C and 20 °C DD 10 °C and 20 °C	Melatonin secretion with a higher amplitude was found at 20 °C than at 10 °C. No rhythm in melatonin was observed at 10 °C under DD, while a circadian-like pattern was observed at 20 °C	Zachmann et al. (1992)
Sea lamprey (*Petromyzon marinus*) (*In vitro* culture of the pineal organ)	10 °C and 20 °C	The amplitude of melatonin rhythm was reported to be temperature-dependent where high amplitude was found at 20 °C than at 10 °C. Melatonin peak was higher at 20 °C than at 10 °C, although melatonin amount declining steadily at night at 10 °C	Zachmann et al., (1992) Bolliet et al. (1993)
Pike (*Esox lucius*) (Pineal organ culture)	12L-12D and constant darkness (DD) photoperiod, and temperature cycle high (10 °C) and low (4°C)	Melatonin secretion was found to be high during the dark phase and low during the light phase under both cold light/warm dark and warm light/cold dark conditions, whereas under a warm light/cold dark cycle the amplitude of melatonin rhythm was found to be reduced	Falcon et al. (1994)
Pike (*Esox lucius*) (Retina and pineal organ)	11L-13D condition	The maximal AANAT1 activity in retina occurred at 37 °C and that in AANAT2 activity in pineal organ occurred at 18 °C	Coon et al. (1999)
Trout (*Oncorhynchus mykiss*) (Retina and pineal organ)	12L-12D condition	The maximum AANAT activity was observed in the pineal organ at 12 °C and the retina at 25 °C	Benyassi et al. (2000)
Rainbow trout (*Oncorhynchus mykiss*) (Pineal organ)	LD 13.1:10.9 at 13 °C; LD 14.3:9.7 at 16.5 °C; LD 11.3:12.7 at 13 °C; LD 10.1:13.9 at 9 °C	No circadian rhythm was seen under any condition conditions irrespective of temperature	Masuda et al. (2003)
Rainbow trout (*Oncorhynchus mykiss*) (Pineal organ)	15 °C, 20 °C, 25 °C under DD *In vitro*	The pineal organ of rainbow trout maintained at different temperatures (15 °C, 20 °C or 25 °C) under DD released melatonin with high rates but the amount of melatonin released was temperature-sensitive (highest at 20 °C).	Iigo et al. (2007a)
Sea bream (*Sparus aurata*) and zebrafish (*Danio rerio*) (Pineal organ)	12L-12D 27 °C and 30 °C	The correlation between peak AANAT activity and fish optimal physiological temperature as seen in sea bream (27 °C) and zebrafish (30 °C)	Falcon et al. (2010b)
Carp (*Cyprinus carpio*) (Pineal organ)	16L-8D 12 °C	The temperature can affect melatonin secretion in fish pineal organ by either suppressing or activating the internal oscillator that maintains melatonin rhythm which probably suppresses/ activates the formation of cAMP and AANAT activity in the pineal organ.	Popek and Cwioro (2010)
Arctic char (*Salvelinus alpinus*) (Pineal organ culture)	8L-16D 0 °C to 45 °C 0 °C to 35 °C	The maximum melatonin secretion was observed in the pineal organ at 20, 25 and 30 °C compared to that cultured pineal organ at higher (45 °C) or lower (0°C) temperatures. No melatonin secretion was observed at 40 and 45 °C Maximum melatonin peak was observed from 0 to 15 °C and minimum melatonin peak was observed from 15 to 35 °C	Cazamea-Catalan et al. (2013)
Catfish (*Clarias gariepinus*) (Pineal organ)	15 °C, 25 °C, and 35 °C under a common photoperiod (12L-12D) during summer and winter seasons	*Aanat2* gene expression was found to be higher during summer as compared to winter under all temperatures with peak expression occurring at 24:00 h during summer and at 21:00 h during winter. The maximum and the minimum of both amplitude and mesor of *aanat2* gene expression rhythm were recorded at 25 °C and 15 °C, respectively	Singh et al. (2017)

of melatonin production in salmonids might enable these species to adapt to extreme environment. Additional comprehensive studies on expression of core clock genes in the pineal organ of salmonids might be of immense help in understanding the molecular basis for the absence of the circadian clock (Iigo et al., 2007a).

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