Role of Kisspeptin, Serotonin, Melatonin in Pubertal Onset of Teleost: Review on Recent Advancements

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Abstract

Freshwater fishes are an important part of many countries' economies as it is a huge part of the aquaculture industry. But due to its detrimental effects on growth performance, sexual behaviour and health, precocious puberty or delayed puberty are some of the reasons the aquaculture business is having issues. Puberty is controlled by various environmental (exogenous) and internal regulatory mechanisms (endogenous). However, the exact mechanism is not yet known. Internal components like the hormones of the central reproductive axis (Gonadotropin-releasing hormone, Follicle stimulating hormone, Luteinizing hormone, Estrogen and Testosterone), peptides like Neurokinin B and Kisspeptin, Leptin, photoperiod hormone Melatonin, neuroendocrine transmitters (Serotonin, Dopamine, Gamma-aminobutyric acid), are to name a few which are involved in the onset of puberty. Knowing the mechanism would help to control the pubertal onset in fish which would ultimately help in the growth of the aquaculture industry. Recently three molecules – Kisspeptin, Melatonin and Serotonin, have come to light which are involved during the pubertal onset. It is observed that Kisspeptin acts as a gatekeeper of the GnRH hormone, Melatonin levels decrease during the pubertal onset time and Serotonin has a role in GnRH secretion and gonadal maturation. The present review focuses on the advancements made in this field by elucidating the central players

(Kisspeptin, Melatonin and Serotonin) working in the diencephalon region of the brain of teleost.

Keywords

pubertal onset, teleost, kisspeptin, melatonin, serotonin, aquaculture.

Introduction

Freshwater fishes (e.g., Tilapia, Rohu, Catla, Carp, Mrigal, etc.) form an important element in the economy of many nations as they have long been a staple item in the diet of many people. That is why the aquaculture sector is growing expeditiously in animal food production and is considered to be a sustainable solution to world food security. The freshwater aquaculture industry accounts for more than 95% of the total aquaculture production[1].

For the aquaculture industry to grow, it is vital that the fish breeds and reproduces properly. The breeding period of fishes is varied in India and reproduction is a periodic phenomenon that is controlled by environmental (exogenous) as well as internal (endogenous) regulatory mechanisms.

Environmental factors like photoperiod, water temperature, feed intake, nutrition, stress, endocrine disruptors, etc. influence the timing of puberty. Light and temperature cue the seasonal breeders to adjust their breeding time to the most appropriate season. For example, in the Atlantic salmon (*Salmo salar*), their spawning depends on light and water temperature. This again depends on the larval development and its first food intake which should optimally occur in spring. Lower water temperature is favourable as compared to high water temperature for successful spawning[2]. Fish species like Barbel (*Barbus barbus*), Tench (*Tinca tinca*) and Chub (*Leuciscus Cephalus*) show pubertal development during the summer which has long days (more photoperiod)[3] while Atlantic cod (*Gadus morhua*) show pubertal development in short days (less photoperiod). Other factors like salinity, swimming frequency (migration), rain period and social communication also play a role in the pubertal onset but are far less studied. For example, Eels can reproduce only once a year after a long migration. It is still unclear how

reproduction is controlled in them, although prolonged swimming might play as a stimulus for the onset of puberty[4].

One of the significant endogenous factors that controls reproduction is the molecular mechanism (sex steroid feedback mechanism) in which comes the highly conserved central reproductive axis, called the Hypothalamic-Pituitary-Gonadal (HPG) axis. In this, the Gonadotropin-releasing hormone (GnRH) is released from the hypothalamus, stimulating the production and release of pituitary glycoprotein hormones, the gonadotropins - luteinizing hormone (LH) and follicle stimulating hormone (FSH). These gonadotropins then act on the gonads to activate gametogenesis and steroidogenesis by stimulating the release of sex steroids (androgens and estrogens). The GnRH neurons sit on the apex of this axis and control reproduction by integrating information from social and environmental signals with hormonal state[5].

Puberty is a biological transition that vertebrates go through, in which they have certain physiological changes in their body. During this time, they show the first signs of sexual maturity and become capable of reproduction. With the initiation of the HPG axis, puberty also starts in vertebrates (including fishes). In teleost, puberty starts sometime after gonadal sex differentiation[6] which is characterized by the onset of spermatogenesis in males[7] and vitellogenic ovarian development in females[8].

In fish farming, in order to control the onset of puberty, it is important to understand the mechanism that triggers puberty as well as the various factors that govern this process. The factors that control the gonadal development and gamete maturation are well-studied in various fish species, but till date data is scarce in regards to the mechanism of puberty in different fish species. Hence, this review focuses on a few factors which are involved during the pubertal onset in teleost and discusses the progress made till now.

Kisspeptin

As discussed earlier, GnRH neurons are the main hub for the regulation of the reproductive system, but their regulation is intricate. A diverse range of cell types and signaling molecules converge on the GnRH neuron network, either directly or indirectly. GnRH neuron regulators work through G Protein-coupled receptors (GPCRs). One of the most significant

GPCRs in the neuroendocrine control of reproductive function is the kisspeptin receptor and its ligand kisspeptin.

Kisspeptin, encoded by gene *kiss1*, belongs to the Arginine (Arg)-Phenylalanine (Phe)-NH_2 (RF-amide) peptide family[9]. It was originally discovered in 1996 as a metastasis suppressor gene in human melanomas and was known as metastin[10]. Following the discovery of kisspeptin, an independent research done in 1999 discovered an orphan receptor GPR54 in rats, which belonged to the rhodopsin family and had a partial sequence resemblance (45%) to the galanin receptor family, but no binding affinity[11]. It was not until 2001 when GPR54 was deorphanized that it was characterized that *kiss1* acts as the endogenous ligand and binds and activates GPR54. Therefore, it was then designated as *kiss1r*[12, 13].

In 2003, there was a breakthrough in the field of reproductive neuroendocrinology when two independent studies linked kisspeptin with the onset of puberty. It was observed that mutation in the *kiss1r* gene caused the impaired onset of puberty and hypogonadotropic hypogonadism in humans[14, 15]. Similar results were also observed in mice when *kiss1* and *kiss1r* genes were mutated[16]. Since then, several studies have been conducted, both in mammalian vertebrates and non-mammalian vertebrates, to understand the physiological role and the mechanistic action of kisspeptin in the control of reproduction.

In 2004, the first non-mammalian *kiss1r* gene was discovered in Tilapia (*Oreochromis niloticus*)[17]. Another paralogous kisspeptin encoding gene, *kiss2*, has also been identified in Zebrafish (*Danio rerio*) and Medaka (*Oryzias latipes*)[18] which has amino acid differences at three positions compared to *kiss1*. Following this, the non-mammalian *kiss1/kiss2* gene was then identified in different fish species like Zebrafish[19], Medaka[20], Sea bass (*Dicentrarchus labrax*)[21], Goldfish (*Carassius auratus*)[22], Senegalese sole (*Solea senegalensis*)[23], chub mackerel (*Scomber japonicas*)[24], Catla (*Catla catla*)[25] and Rohu (*Labeo rohita*)[26]. Species-specific differences arise, where some species have both the forms present (e.g., Zebrafish, Medaka, Goldfish, Sea bass, Chub mackerel, Rohu) and whereas some species have only one form (e.g., Tilapia, Senegalese sole). It is evident from all of these investigations that the amino acid sequences are highly conserved, and they also provide evidence that the *kiss1/kiss1r* system is a trait that all vertebrates have maintained throughout evolution except birds. Other than the brain, kisspeptin is also found to be expressing in other tissues like gonads and adipose tissue, nevertheless, their tissue-specific role is yet to be explored.

Anatomical distribution of kisspeptin neurons and its receptors

Two populations of *kiss1* neurons have been observed: [1] In Zebrafish, Medaka[18], Goldfish[27] and Sea bass[28] *kiss1* is found in the ventral habenula. [2] Another population has been observed only in medaka[18, 20] is present in the nucleus posterioris periventricularis (NPPv) and the nucleus ventral tuberis (NVT).

kiss2 has been observed only in a hypothalamic nucleus, the dorsal zone of the periventricular hypothalamus (also designated as the nucleus recessus lateralis, nRL) in the Tilapia[29], Zebrafish, Medaka[18, 30], Goldfish[27] and Sea bass[28]. A second population has also been found in Goldfish and Zebrafish in the pre-optic region (POA)[27, 31].

In Chub mackerel both *kiss1* and *kiss2* are found in the anterior POA and hypothalamus (NLT and the nRL region)[32].

The receptors (*kiss1r* and *kissr2*) of the genes (*kiss1* and *kiss2*) are found to be expressing at the same location where the genes are present. This suggests that there is an autocrine regulation of the genes.

Species	**Habenula**	**Preoptic region**	**Hypothalamus**		
			nPT/NPPv	**Hd/nRL**	**Hv/NVT/nLT**
Zebrafish	*kiss1*	*kiss2*	*kiss2*	*kiss2*	
Medaka	*kiss1*		*kiss1*	*kiss2*	*kiss1*
Goldfish	*kiss1*	*kiss2*		*kiss2*	*kiss2*
Tilapia				*kiss2*	
Sea bass	*kiss1*			*kiss2*	
Chub mackerel		*kiss1, kiss2*		*kiss1, kiss2*	*kiss1, kiss2*

Table 1: Distribution of kisspeptin cells in the brain of teleost

nPT/NPPv: posterior tuberal nucleus/nucleus posterioris periventricularis; Hd/nRL: dorsal zone of periventricular hypothalamus/nucleus recessus lateralis; Hv/NVT/nLT: ventral zone of periventricular hypothalamus/nucleus ventral tuberis/nucleus lateralis tuberis.

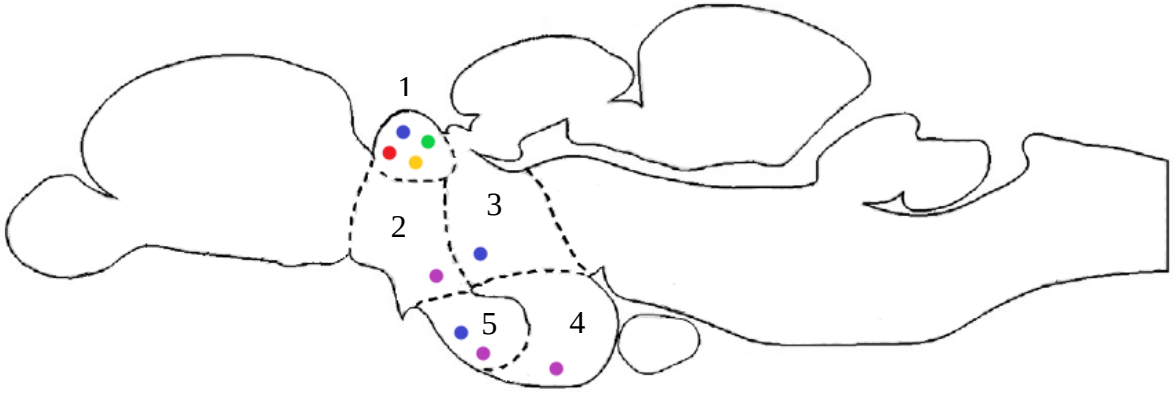

Figure 1: Distribution of kiss1 cells in the brain of teleost

1-Habenula, 2-Preoptic region, 3-nPT/NPPv, 4-Hd/nRL and 5-Hv/NVT/nLT. Red-Zebrafish, blue-Medaka, yellow-Goldfish, green-Sea bass and purple-Chub mackerel.

Figure 2: Distribution of kiss2 cells in the brain of teleost

1-Habenula, 2-Preoptic region, 3-nPT/NPPv, 4-Hd/nRL and 5-Hv/NVT/nLT. Red-Zebrafish, blue-Medaka, yellow-Goldfish, pink-Tilapia, green-Sea bass and purple-Chub mackerel.

Physiological action of kisspeptin

In a study done in 2004 in the brain of Tilapia fish, it was observed that the expression of *kiss1r* increases during the time of pubertal onset, which subsequently decreases after exposure to continuous light[17]. These findings also suggested that light may have an impact on the transcriptional processes controlling the *kiss1r* expression. In 2008, gene expression studies

done in Zebrafish revealed that levels of *kiss1r* mRNA in the brain rise sharply at the start of puberty, indicating that the *kiss1/kiss1r* pathway contributes to the onset of puberty in fish like that of in mammals. The study also suggested that kisspeptin has a role in reproduction as it was also found to be expressing in the gonads[19]. Increased expression of kisspeptin was also observed in the brain and gonads of Olive flounder (*Paralichthys olivaceus*) during the onset of puberty[33]. In Catla fish, after injecting with nano-encapsulated kisspeptin, an increase in the expression pattern of reproductive genes (GnRH, LH and FSH) was observed, which ultimately led to the onset of puberty[25]. Similar results were observed in Nile Tilapia, where the *kiss2* expression was significantly higher at the immature stage than the mature stage, suggesting its involvement in the gonadal development. Also, administering kisspeptin externally resulted in elevated estradiol and testosterone levels in blood plasma and GnRH, and gonadotropin expression in the brain[34]. Recently in 2020, an intramuscular injection of kisspeptin was given to Senegalese sole and it resulted in the increase of gonadotropin synthesis and secretion, as well as the testosterone plasma titers[35].

Kisspeptin & GnRH

A study done by Parhar in 2004 in Tilapia fish showed the co-expression of kisspeptin in GnRH neurons, which offers the first proof of a connection between kisspeptin and the GnRH system[17]. Following that, studies done in Grey mullet (*Mugil cephalus*)[36], Cobia (*Rachycentron canadum*)[37] and Fathead minnow (*Pimephales promelas*)[38] have established that *kiss1r* expression in the fish brain is localised to GnRH neurons and is higher in fish at the beginning of puberty compared to pre or post-puberty, at a time when GnRH expression is also elevated. These results offer preliminary proof that kisspeptins directly target GnRH cells in fish and that they likely cause the release of GnRH during puberty by interacting with *kiss1r*, as is the case in mammals. Gnrh1 neurons are found to be expressing *kiss2r* in Burtoni fish (*Astatotilapia burtoni*)[39] and Stripped bass (*Morone saxatilis*)[40]. A positive correlation of kisspeptin-GnRH was also reported in Zebrafish[41], Chub mackerel[42], Sea bass[43] and Chinese sucker (Myxocyprinus asiaticus)[44]. To ascertain the precise physiological function of the GnRH-kisspeptin system in fish, however, a far more thorough understanding of the expression of *kiss1r* and *gnrh* concerning pubertal onset is an area of research.

Kisspeptin on pituitary level

Although the hypothalamus is the main action centre for kisspeptin to control puberty by regulating GnRH secretion, in mammals evidence suggests that it can also affect the pituitary directly as its mRNA expression has been observed there. *In-vivo* experiments have been conducted on pre-pubertal Sea bass by administering kisspeptin and checking its effect on the GTH (pituitary hormones) secretion. Results reveal that LH and FSH secretion was induced by both kisspeptins, while *kiss2* exhibits a more pronounced response to activation than *kiss1*[45]. The opposite was observed in Goldfish where *kiss1* induced the LH secretion *in-vivo* but no significant expression *in-vitro*, whereas *kiss2* had no effect on LH in both *in-vivo* and *in-vitro*[22]. In female Zebrafish it was found that after administration of both *kiss1* and *kiss2*, it was found that *kiss2* (and not *kiss1*) increases the FSH and LH expression in the pituitary[18]. There are also reports which show an inhibitory role on LH expression in the European eel (*Anguilla anguilla*) but not on FSH expression[46]. Another report found that after giving kisspeptin injections to the fishes, it accelerated their puberty by showing advancement in spermatozoa and oocyte development in males and females respectively[47]. But again, another report in Sea bass found that *kiss1* had no effect on gonadotropin release but *kiss2* induced the secretion[43]. From these reports, we can say that the role of kisspeptin on the pituitary level is conflicting and needs further studies.

The presence of the kisspeptin system in the brain of fish provides a solid base to perform further studies to demonstrate the claimed central role in the control of puberty and thus reproductive function.

Apart from kisspeptin, the other key player which accounts for puberty is the neuroendocrine transducer, melatonin.

Melatonin

Fishes are either irregular or seasonal breeders. For a brief period of time, they are engaged in their peak reproductive activity or breeding which is followed by an intricate preparation process. To ensure that the breeding takes place during the most advantageous time of the year, recurrent reproductive events frequently coincide with the seasonal changes in a group of environmental cues (as discussed earlier)[48]. The circadian clock is synchronized and modulated by environmental cues, and this in turn affects the rhythmic generation of messengers that act on target cells and tissues to regulate various bodily activities[49]. This biological/circadian rhythm is sensed and managed by the eye (retina) and the pineal gland.

The fish pineal organ is regarded as the most significant element of the neuroendocrine system due to its special ability to directly respond to changes in environmental light-dark circumstances. The primary role of the pineal gland is to take information about the environment's status of the light-dark cycle and transmit it so that the hormone melatonin can be produced and secreted[50].

Melatonin is a lipophilic molecule that is synthesized from tryptophan amino acid. A prerequisite for melatonin synthesis by five enzymatic reactions is the uptake of tryptophan from the circulation into the pineal gland, and arylalkylamine N-acetyltransferase (AANAT) is the penultimate rate-limiting enzyme in this biosynthetic pathway. When the AANAT gene is expressed in the pinealocytes of the pineal organ, the adrenergic system is used as a response mechanism to changes in environmental light-dark conditions. Melatonin is then synthesized and released into the bloodstream to carry out its final hormonal actions on the target cells, tissues, and organs[51, 52].

Melatonin is used to determine recurrent reproductive events in an annual cycle by measuring and predicting daily and seasonal time. Plasma melatonin titers stay high during the dark phase (night) and low during the daylight in fish, as they do in other vertebrates, where melatonin functions as a conservative chemical messenger of photoperiod or *Zeitgeber*[53]. Because of this characteristic, it is also termed as “signal of darkness” or the “time-keeping hormone”[54]. Throughout evolution, the mechanism of photoperiodic or circadian control of melatonin production in the pineal gland has undergone significant change, yet the melatonin signal released into the blood is the same in fish and mammals[55].

Researchers have focused on how melatonin regulates reproduction in a wide range of fish species as a powerful photo-neuroendocrine signal from the pineal organ. According to the theory developed from various fish research, melatonin interacts with the hypothalamus to affect the reproductive system. To integrate the photoperiodic information, the preoptic area (POA) of the hypothalamus in fish receives nervous inputs from the retina and the pineal organ, among them the hormonal (melatonin) input from the pineal organ plays a crucial role in the photo-neuroendocrine control of fish reproduction[55].

Melatonin receptors

In fishes, three forms of melatonin receptors are found: MT1 (*mtnr1a*), MT2 (*mtnr1b*) and MT3 (*mtnr1c*). They are found to be present in the retina and different parts of the brain (POA telencephalon, diencephalon and in the pituitary)[56]. However, the exact role of these receptors during pubertal onset in fish remains elusive. A study done in Nile tilapia found the MT1 receptor to be most associated during the onset of puberty[57].

Melatonin, kisspeptin and GnRH

It is known that European sea bass exhibits day-night fluctuations and that melatonin inhibits the expression of GnRH and its receptors in the brain[58]. There is co-expression of *kiss1* and *kiss2* neurons and the melatonin receptors found in the lateral tuberal nucleus and the parvocellular preoptic nucleus region of the brain in Sea bass[28, 59]. The findings of the Zebrafish study, which demonstrate the receptor-mediated action of melatonin at the brain level, suggest that melatonin may promote the release of hypothalamic GnRH by likely involving the *kiss1r* system in the GnRH neurons[60]. Although it has been shown that melatonin plays a significant part in the transduction process of photoperiodic signals in the regulation of seasonal reproduction, kisspeptin cells do not appear to express the melatonin receptor, therefore it is still unclear how seasonality alters kisspeptin activity[61]. It was found that in Orange-spotted grouper (*Epinephelus coioides*), the down-regulation of melatonin receptor (which is more expressed at night and less expressed in the day) resulted in up-regulation of *kiss2* and GnRH (which is more expressed in the day and less expressed in the night)[62]. The results of a recent study on Goldfish, however, suggested that melatonin's light-mediated effects to regulate sexual development in fish may be the result of interactions between melatonin, GnIH, and Kiss[63]. In European sea bass, a study was conducted to look into whether essential genes that activate the HPG axis can be activated by the light stimulus integrated by clock proteins. It was found that the clock genes (*clock, npas2* and *bmal1*) and the genes *kiss*, *kissr* and *gnrh* shared conserved transcription factor frameworks in their promoters. This indicated that there might be a correlation between them[64]. Furthermore, in the hypothalamus region (diencephalon) of the Cinnamon clownfish (*Amphipirion melanopus*), GnIH (an antagonist of GnRH) and the melatonin receptor were found to be co-localized[65].

Substantial evidence from studies[66, 67, 68, 69] suggests that to activate the reproductive axis, melatonin levels must either rise or fall. In mammals, it has been found that melatonin secretion reaches its lowest levels at the time of puberty. If there is excessive melatonin secretion, then there is a delay in the onset of puberty[67]. It was also observed that by giving

melatonin, it reduces the expression of kisspeptin under conditions of prolonged photoperiod[68], while endogenous melatonin suppression (after pinealectomy) abolishes the effects of reduced photoperiod on kisspeptin expression[69]. So, from these studies, it can be said that because of melatonin, the kisspeptin hormone remains suppressed before the pubertal period, and during puberty, the decrease of melatonin results in the release of kisspeptin which in turn activates the HPG axis.

The research on melatonin is more emphasized with respect to reproduction. Not many studies have been done to check its functional role during the onset of puberty in fish. But from the existing reports, we can say that melatonin might have an indirect activity with both kisspeptin and GnRH. Thus, studies need to be carried out in this area so that the role of Melatonin and its crosstalk with kisspeptin become evident in the onset of puberty.

For the control of reproduction in vertebrates, the endocrine and the nervous system work together (neuroendocrine). We have already discussed above the prime factors involved in it, i.e., the environmental factors, GnRH, kisspeptin and melatonin. In addition to them, the monoamine neurotransmitter serotonin (5-hydroxytryptamine) is also involved in reproductive functions.

Serotonin

Serotonin is the precursor of melatonin and is synthesized from L-tryptophan, an essential amino acid, with the assistance of two enzymes: tryptophan hydroxylase (TPH) and amino acid decarboxylase[70].

Anatomical distribution of serotonin and its receptors in the brain of teleost:

Studies have shown three major serotonergic populations in the brain of teleost: (i) pretectal population, (ii) posterior tuberculum/hypothalamic populations, and (iii) raphe populations[71, 72]. Serotonin receptors have been identified in various fishes such as Zebrafish[73], Tilapia, Rainbow trout (*Oncorhynchus mykiss*), etc. Three serotonin receptor subtypes (5-HT1, 5-HT2, and 5-HT7) have been found in Zebrafish, including two subtypes (5-HT2A and 5-HT2C) of 5-HT2 and three subtypes of 5-HT1 (5-HT1aa, 5-HT1ab, and 5-HT1bd)[74, 75]. 5-HTr1aa, 5-HTr1ab, and 5-HTr1bd are predominantly expressed in the preoptic area and hypothalamus of the Zebrafish brain[74], while 5-HT2C is expressed in the telencephalon, diencephalon, rhombencephalon, and spinal cord[75]. In addition to these, serotonin cells are also

found in the pineal gland[72], suggesting a possible interaction between serotonin and melatonin during the pubertal onset.

Functional role of serotonin

According to an immunohistochemical investigation, Serotonin fibres closely associate with GnRH neurons in the hypothalamus and olfactory bulb of the Atlantic croaker (*Micropogonias undulatus*)[76]. In Zebrafish, serotonin receptors are expressed in a number of brain regions that contain GnRH neurons, which suggests that GnRH may co-express with serotonin receptors, as shown in mammals[74, 77]. Studies conducted on teleost in both *in-vitro* and *in-vivo* environments have demonstrated the role of 5-HT1 or 5-HT1 receptor subtypes in promoting gonadotropin secretion[78, 79, 80]. Serotonin and GnRH promote LH secretion in the Atlantic croaker[80]. In cultured brain preoptic-anterior hypothalamic area and pituitary fragments of Goldfish, serotonin promotes the release of GnRH[81]. In Prussian carp (*Carassius gibelio*), serotonin alone had no effect on the spontaneous release of LH, but when GnRH analogue was co-administered, serotonin's additive effects were seen[82]. These findings point to a functional link between the GnRH and serotonin systems in teleost.

Conclusion

From the existing studies, we can say that the three components - kisspeptin, melatonin and serotonin are closely associated with the reproductive endocrine signalling pathways and somehow control the onset of puberty. Till now individual studies of these components have been done with respect to the onset of puberty. Only a few studies are found linking kisspeptin and melatonin. However, no research has discussed how serotonin affects the kisspeptin system in vertebrates. Therefore, further analysis needs to be done to understand how these three interacting players affect each other, which will further help to elucidate the mechanism of puberty. Advanced techniques like transcriptomics will help in deciphering the expression profile of key molecules playing a role during the onset of puberty. Additionally, thorough research is needed in understanding the mechanism of the onset of puberty which can be extrapolated as an application to the aquaculture industry.

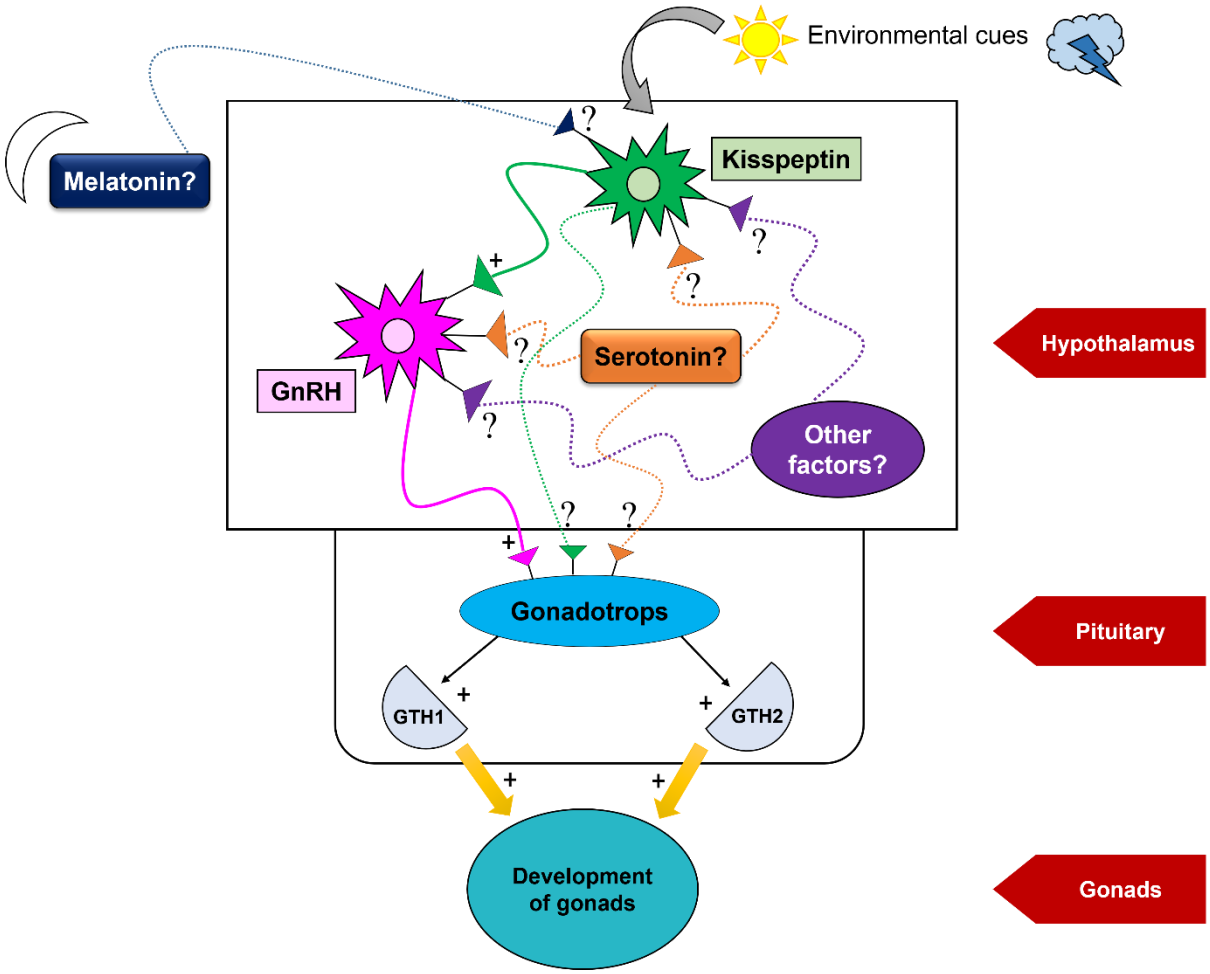

Figure 3: Summary diagram of the possible interaction between kisspeptin, melatonin, serotonin and other factors in fish during the onset of puberty.

Environmental cues are interpreted by the kisspeptin neurons present in the hypothalamus and they activate the GnRH neurons, initiating the HPG axis. How melatonin, serotonin and other factors contribute to it is yet to be understood. Potentially, they may bind with the kisspeptin or GnRH neurons in the hypothalamus or may directly bind with the Gonadotrops at the pituitary level.

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Glossary

Endocrine Disruptors- They are chemical substances that can interfere with the normal functioning of the endocrine system, disrupting hormone production and regulation in humans and other organisms.

Gametogenesis- process by which sperm and eggs are produced from the germ cells in the testes and ovaries, respectively.

Steroidogenesis- the biological process by which specialized cells, typically located in the adrenal glands and gonads (ovaries and testes), synthesize and produce steroid hormones. These hormones include hormones like cortisol, aldosterone, testosterone, and estrogen, which play essential roles in various physiological processes such as metabolism, immune response, and reproductive functions.

G protein-coupled receptor (GPCR)- are a large family of cell surface receptors that transmit signals from the extracellular environment to the inside of the cell. They are involved in a wide range of cellular processes and play a crucial role in mediating the effects of various hormones and neurotransmitters.

Hypogonadotropic hypogonadism- is a medical condition characterized by abnormally low levels of sex hormones, such as testosterone in males and estrogen in females, due to a deficiency of gonadotropin-releasing hormone (GnRH) or the failure of the pituitary gland to produce sufficient amounts of gonadotropins (LH and FSH). This hormonal imbalance leads to impaired development and functioning of the gonads (testes in males and ovaries in females), resulting in delayed or absent puberty and reduced fertility.

Circadian- refers to biological processes or behaviors that exhibit a rhythmic pattern with a cycle of approximately 24 hours. These processes are influenced by the internal biological clock in organisms, which helps regulate various physiological and behavioral changes, such as sleep-wake cycles, hormone production, body temperature, and metabolism, in alignment with the day-night cycle.

Zeitgeber- A zeitgeber is an external cue or time cue that helps to synchronize an organism's internal biological rhythms, particularly the circadian rhythm, with the natural 24-hour day-night cycle. Common zeitgebers include light, temperature, social cues, and feeding times,

which can influence an organism's internal clock and help it adjust its physiological and behavioral activities to the appropriate time of day.