REVIEW / ARTÍCULO DE REVISIÓN

Hormonal and neuroendocrine control of reproductive function in teleost fish

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Abstract: Reproduction is one of the most important physiological events for the maintenance of the species. Hormonal and neuroendocrine regulation of teleost requires multiple and complex interactions that take place along the hypothalamic-pituitary-gonad (HPG) axis. Within this axis, gonadotropin-releasing hormone (GnRH) regulates synthesis and release of gonadotropins, follicle stimulating hormone (FSH) and luteinizing hormone (LH). Steroidogenesis drives reproduction function in which the development and differentiation of gonads. In recent years, new neuropeptides have become the focus of reproductive physiology research as they are involved in the different regulatory mechanisms of the growth, metabolism, and reproduction of these species. However, especially in fish, the role of these neuropeptides in the control of reproductive function is not well studied. The study of hormonal and neuroendocrine events that regulate reproduction is crucial for the development and success of aquaculture.

Key words: Hormonal control, neuroendocrine, reproductive function, teleost fish, aquaculture.

Introduction

Aquaculture is the fastest-growing food production sector globally and plays an essential role in meeting the food demand of populations. In this stage, incorporating new technologies that allow increasing the number of cultivable species is crucial[1,2]. For several years, the aquaculture sector has focused mainly on establishing the minimum requirements for the development, growth, and reproductive success of the different species[3,4]. The study of endocrinology in teleost fish has been fundamental for understanding the functional roles of hormones in biological systems. In recent years, the existence of a complex and infinite number of interactions between hormones and nerve structures has been demonstrated[5-9]. Reproduction is one of the most important biological processes of organisms since the survival and perpetuation of the species depend on it[1,10]. The control of reproductive events allows the application of selection programs to improve the growth rate, the survival of the species, reduce the problems associated with sexual maturation and generate monosex populations[11,12]. The quality of spawning depends on environmental factors such as photoperiod, temperature, salinity, tank volume, substrate vegetation, etc[1,13]. The initiation of reproduction is affected by the number of energy reserves in the body and is sensitive to various metabolic factors.

The neuroendocrine mechanisms responsible for the association between energy balance and fertility are represented by metabolic hormones and neuropeptides that affect the hypothalamic center. In teleosts, as in other vertebrates, reproduction is coordinated by the hypothalamic-pituitary-gonad (HPG) axis[14-16]. However, there is very little research on reproductive biology and these species' molecular and cellular mechanisms[12,17,18]. This review presents a general bibliographic compilation of the main hormonal and neuroendocrine aspects of the control of reproductive function in teleost fish. Therefore, it will try to provide an overview of the most significant findings in recent years.

Hormonal control of reproduction in teleost fish

The control of reproduction in fish is a multifactorial process involving environmental, social, neuronal, endocrine, and metabolic agents. a cascade of hormones regulates[19,20] reproduction. The mechanisms involved in this process depend on the HPG axis (Figure 1)[15,16]. Hormones and neuropeptides are produced in specific neuronal regions of the brain, mainly in the hypothalamus. These can directly inhibit or stimulate gonadotropins (GtH) release into the bloodstream or indirectly through their functions on gonadotropin-releasing hormone (GnRH)[21,19]. The beginning of sexual maturation in fish presents two simultaneous events: the release of gonadotropin-releasing hormone (GnRH)[22-25] and the activation of GtH receptors in the gonads[26]. The activation of these receptors stimulates the production of germ cells, the synthesis of sex steroids and growth factors, and the effectors of gonadal development[12,27,19]. At the level of the pituitary gland, different molecules are secreted, such as: luteinizing hormone (LH), follicle-stimulating hormone (FSH), growth hormone (GH), prolactin (PRL), thyroid-stimulating hormone (TSH), among others[21]. These hormones participate in osmoregulation processes, growth, gonadal steroid production, the onset of pu-

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berty, and reproductive behavior of fish[7,12,28-30]. In addition, a series of neuroendocrine factors and hypothalamic neuropeptides have been identified that regulate behavior, eating, and energy balance. Their physiological and metabolic functions guarantee survival and growth during the reproductive stage[16]. Within these neuropeptides, we can mention the GH releasing hormone (GHRH), pituitary adenylate cyclase-activating polypeptide (PACAP), Somatostatin (SS), the thyrotropin-releasing hormone (TRH), Dopamine, Neuropeptide-Y (NPY), gamma-aminobutyric acid (GABA), neurokinin B (NKB) and gonadotropin inhibiting hormone (GnIH)[18,31-36]. In addition, among these neuropeptides is also included Kisspeptin (Kiss)[37], which constitutes an important regulator of the synthesis and release of GnRH[38,39,40,41]. Another very novel neuropeptide is Phoenixin (PNX), which regulates physiological processes such as food consumption, proliferation, and cell differentiation[42,43]. Moreover, it has been reported to be involved in reproductive function; due to its role in gene expression regulation in the hypothalamus and pituitary[44,45]. High concentrations of phoenixin in the central and peripheral nervous systems suggest that the peptide may serve as a multi site-directed signaling molecule[44,46,47]. In general, these brain factors, in addition to being involved in the secretion of pituitary hormones, regulate other physiological systems, but they greatly influence reproduction[12,30,36,48]. At each level of the axis, a limited number of target cells are under the influence of many factors. The final cellular response is the overall effects of these mediators on the components of intracellular signal transduction[49]. Mature gonads secrete sex steroids (estrogens and androgens), which negatively regulate hormonal secretions in the hypothalamus and pituitary gland. This closed-loop system maintains the homeostasis of the reproductive system[12]. In general, according to their functions on the reproductive cycle, FSH has a vitellogenin function and LH a maturational function[50-53].

Gonadotropin-releasing hormone (GnRH)

In fish, as in all vertebrates, reproduction is regulated by the hypothalamus through gonadotropin-releasing hormone (GnRH)[16,54]. This hormone constitutes the critical element of the neuroendocrine control of reproduction[16,55-58]. The (GnRHs) constitute a family of peptide molecules whose nature and diversity have been evidenced in teleost fish[59]. Three structural variants of GnRH have been identified in various vertebrate species: GnRH1, GnRH2, and GnRH3[56,57,58,60,61]. However, the molecular mechanisms that link the 3 isoforms of GnRH with reproduction in fish are not well clarified[62].Mammals only possess GnRH1 and GnRH2, while teleost fish have two or all three types of GnRH[41]. Most teleost fish, including Perciformes and Pleuronectiformes, present all three GnRH isoforms[36,55,57,63]. Other fish species such as salmon (*Salmoninae*), zebrafish (*Danio rerio*) and goldfish (*Carassius auratus*) possess only two forms of GnRH (GnRH2 and GnRH3)[14,36,64,65] GnRH1 is expressed mainly in the olfactory bulb, ventral telencephalon, and the pre-optic zone. GnRH2, a conserved form from fish to mammals, is expressed mainly in the midbrain[36].

GnRH3 constitutes the specific form of GnRH in fish[66,67] and has a similar distribution to GnRH1. The three structural variants of GnRH have different physiological functions.

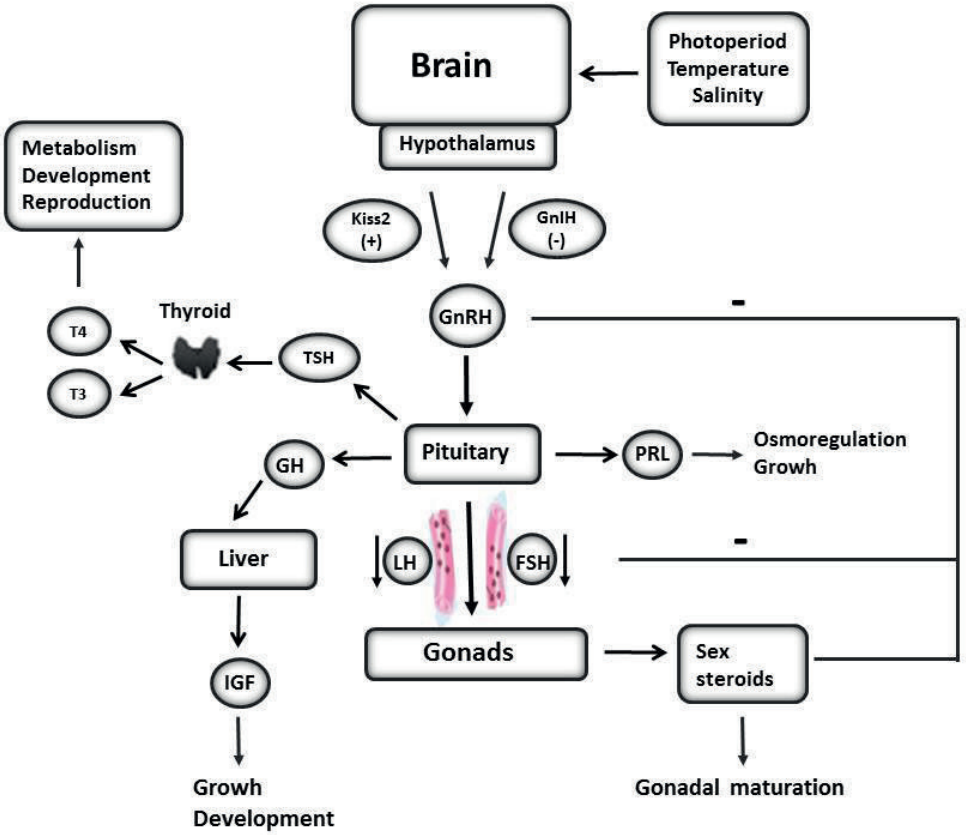

Figure 1. Hypothalamic-Pituitary-Gonads (HPG) axis. Gonadotropin-Releasing Hormone (GnRH); follicle-stimulating hormone (FSH); luteinizing hormone (LH); prolactin (PRL); growth hormone (GH); Kisspeptin (Kiss2); Gonadotropin inhibitory hormone (GnIH); Growth factors (IGF); Thyroid-stimulating hormone (TSH); Triiodothyronine (T3); Tetraiodothyronine (T4). GnRH secretion acts on a population of gonadotropic cells of the pituitary, which release LH and FSH. In addition, the pituitary is the site of synthesis, storage, and release of GH, TSH, and PRL; it is considered a transducer that, through its secretions, regulates endocrine functions, such as reproduction, osmoregulation, growth, and metabolism.

GnRH1 is considered the hypothalamic variant capable of stimulating gonadotropin secretion and constitutes the fundamental regulator of the pituitary in mammals[56,58]. In teleost fish, GnRH1 has its physiological importance in the regulation of gonadotropin secretion and gametogenesis[14]. GnRH2 is involved in regulating eating behavior[58,68,69,70,71] and probably has an intermediary role between food intake and reproduction[72,73]. It is highly probable that both GnRH2 and other GnRH isoforms expressed in the olfactory region play a role in the perception of social and pheromonal signals[36,74]. GnRH3 participates in the control of reproductive behaviors in several fish species[14] .For example, this isoform stimulates the nesting behavior of male dwarf Gourami (*Trichogaster lalius*)[14]. In adult zebrafish lacking GnRH3 neurons, there was evidence of an arrest in oocyte development and also a reduction in the mean diameter of the oocytes. These findings suggest that hypophysiotropic GnRH3 neurons are critical for normal oocyte development and reproduction[75]. Both this study and those carried out by Palevitch *et al.* 2007[76], suggest that GnRH3 is the hypophysiotropic GnRH capable of regulating the HPG axis in species lacking GnRH1, such as zebrafish. The action of GnRHs on target cells is mediated by specific binding to their membrane receptors (GnRHR)[36]. Corresponding to the primary role of GnRH in controlling reproduction, GnRHRs are mainly localized in the brain to mediate the neuromodulatory actions of GnRH in other neuronal systems and in gonadotropic cells of the pituitary to regulate gonadotropin secretion. Furthermore, GnRHRs, like GnRHs, are found in the gonads and other peripheral tissues, exerting multiple physiological actions[36,77]. In general, the primary function attributed to GnRH is the stimulation of the synthesis and release of GtH in teleost fish[36,55,77-81] Besides, it can regulate the gonadal maturation, the development of germ cells (oogenesis and spermatogenesis), gonadal steroid production, ovulation, spermiation, and spawning[36,57] In addition, it is involved in the control of the release and expression of growth hormone, somatolactin, and prolactin[82,83]. Considering the published results in the literature, the effects of GnRHs on the control of reproductive function depend on the species, sex, and reproductive status, as well as the complex endocrine interactions along the HPG axis[57,83].

Kisspeptin

Kisspeptin regulates the HPG axis[34,84,85,86], and in the initiation of sexual maturation[84,87]. Kisspeptin expression is more abundant in the brain, particularly in the hypothalamus[84,88]. It originates from neuronal populations in the hypothalamus and projects into the median eminence (EM) and preoptic area (POA) regions, where GnRH neurons are also found[89,90,91]. However, its expression has been evidenced in peripheral tissues such as the intestine, kidney, liver, pancreas, adipose tissue, and gonads[92]. In mammals, only (*kiss1*) coding for kisspeptin and (kiss1r) coding for the receptor have been identified[93]. However, in some teleost species due to a third duplication of the genome, two genes coding for kisspeptin (*kiss1* and *kiss2*) have been identified[86,93] Some of these species are medaka (*Oryzias latipes*)[84], zebrafish[84,94], sea bass (*Lateolabrax japonicus*), and redfish (*Sciaenops ocellatus*)[95]. Other species, such as the puffer fish (*Takifugu niphobles*)[87] and Senegalese sole (*Solea senegalensis*) contain only the kiss2 gene[96]. The kisspeptin receptor (kiss-R) in fish is expressed in tissues such as the brain, pituitary, gonads, heart, kidney, liver, and muscle[84,87,97-99]. Different teleosts species have two or even three genes encoding for kisspeptin receptors (*kiss1r, kiss2r, kiss3r*)[93,100]. For example, kiss1r and kiss2r have been identified in medaka, zebrafish, goldfish, striped bass (*Morone saxatilis*), and European bass (*Dicentrarchus labrax*). However, kiss2r has only been identified in Nile tilapia (*Oreochromis niloticus*), cobia (*Rachycentron canadum*), gray mullet (*Mullus barbatus*), spotted grouper (*Epinephelus fuscoguttatus*), Senegalese sole, among others[101]. Kiss3r, the expression demonstrated in zebrafish[97], goldfish[102], medaka[103], striped bass (Zmora *et al.*, 2012), and European eel (*Anguilla anguilla*)[104]. There is evidence in fish of the participation of kisspeptins and their receptors in the feedback mechanisms of sex steroids[40]. The role of kisspeptin in reproduction is based mainly on the stimulation of GnRH release, indirectly modulating the release of LH and FSH[93,105]. In mammalian models, kisspeptin regulates the release of LH through projections on GnRH neurons. However, in the case of teleosts, these functions are not clear[62]. Zhao *et al.* 2014[106] provided interesting data on the modulatory effects of kiss1 and kiss2 on neuronal GnRH subpopulations. First, they reported that treatment with kiss1 or kiss2 during the first day after fertilization stimulated the proliferation of GnRH3 neurons in the peripheral nervous system. However, only kiss1 stimulated the proliferation of terminal and hypothalamic nerve populations of GnRH3 neurons[106]. In zebrafish (GnRH3) and striped bass (GnRH1), few preoptic GnRH neurons appear to be innervated by kisspeptin[94,107,108]. However, European seabass (*Dicentrarchus labrax*) and medaka hypothalamic GnRH3 neurons are not associated with kisspeptin fibers[88,109]. Zmora *et al.* 2015[110], found kiss1 immunoreactive nerve endings that reach LH cells, suggesting the existence of a direct pituitary site of action of kisspeptin These results are similar to those published by Shahjahan *et al.* in 2014[14] where the expression of kisspeptin is evidenced in the pituitary gland of goldfish and puffer fish (*Takifugu rubripes*). Studies in goldfish[37,99] and sea bass[111] have confirmed a direct stimulation in the secretion of LH and FSH in pituitary cells in response to kisspeptin administration. On the other hand, in goldfish, kiss1 significantly increased LH-β, GH and PRL mRNA levels through *in vitro* studies[99]. Interestingly, both kiss1 and kiss2 regulate FSH-β expression levels in pituitary cell cultures in striped bass (*Morone saxatilis*). However, only Kiss1 can regulate LH-β mRNA levels in seabass negatively[110]. In sexually mature female zebrafish, administration of Kiss2 by intraperitoneal injection significantly increased FSH and LH mRNA levels. On the other hand, the administration of kiss1 by the same route did not have significant differences in GtH gene expression levels[84,112]. The stronger effect of kiss2 compared to kiss1 was also observed in the release of FSH and LH in sea bass[95,112]. A similar trend was observed for the effects of kisspeptins on the stimulating effect on gonadal maturation in seabass and striped bass[113]. In contrast, intraperitoneal injections of kiss2 stimulated mRNA expression of FSH rather than LH in female spotted grouper[114]. Furthermore, in goldfish, intraperitoneal injections of kiss1, but not kiss2, stimulated the release of LH in sexually mature females[102]. Also, it has been reported that kiss2 may have effects on food intake and growth function[88,96,115]. Furthermore, it can act as a link between food intake, energy homeostasis, and reproduction[116-118]. In general, these findings indicate the role of kiss1 and kiss2 in gonadotropin regulation is species-specific. Collectively, the differences between the species derive from their reproductive behavior and the stages of reproduction.

Gonadotropin inhibitory hormone (GnIH)

Multifactorial control of reproduction also involves other neurohormones such as gonadotropin inhibitory hormone (GnIH)[20]. In fish, GnIH is expressed mainly in the brain and pi-

tuitary, although its expression has also been evidenced in the spleen, gonads, muscle, eyes, and kidney[119-122]. GnIH acts by binding to GnIH receptors (GnIH-R) that belong to the family of G protein-coupled receptors. Two GnIH-Rs (GPR147 and GPR74) have been identified in vertebrates, but only GPR147 appears to be present in fish[122-124]. GPR147 have been identified in fish's central and peripheral tissues, including the brain, pituitary, eyes, heart, intestine, kidney, liver, spleen, muscle, and gonads[125-127]. As its name suggests, the main function of GnIH is the inhibition of gonadotropin release through the inhibition of GnRH and kisspeptin[128,129], an action that has been described in many vertebrates. However, the physiological functions of GnIH in fish are not precise yet. Contradictory effects have been observed in fish, both *in vivo*[130] and *in vitro*[131] For example, administration of GnIH to pituitary cell cultures of mature female Nile tilapia increased LH and FSH mRNA levels[18,130]. It has been shown that in goldfish, GnIH inhibits both the synthesis and the release of gonadotropins in the early stages of gonadal maturation but not in spawning[132]. Administration of GnIH to zebrafish by intraperitoneal injection decreases plasma LH levels in adult goldfish[125,132]. However, the inhibitory effect of GnIH injections was not observed in juvenile stages[132]. *In vitro* studies showed that the administration of GnIH from goldfish stimulates the expression of gonadotropins in pufferfish with apparent seasonal differences in reproduction[132,133]. These findings indicate that, in teleosts, the physiological effect of GnIH on the HPG axis differs between gonadotropin synthesis and release and depends on the reproductive stage. Even though researchers have shown that GnIH exerts both stimulatory and inhibitory actions, depending on the season and species, both GnRH and GnIH are considered essential components of the multifactorial control of reproduction[20].

Gonadotropins (GtHs)

In teleosts, as in all vertebrates, the functions of the gonads are maintained thanks to the actions of the gonadotropins. They have a central role in the regulation of gametogenesis[134] and the steroidogenesis necessary for the development of sexual behavior and secondary sexual characteristics[1,78,80,135]. Gonadotrops are cells specialized in producing gonadotropins such as follicle-stimulating hormone (FSH) and luteinizing hormone (LH). Both are glycoproteins made up of two non-covalently associated subunits (α and β). The α subunit has 92 amino acids (aa) and is common in both gonadotropins. The β subunit has 121 aa for LH and 118 aa for FSH. This subunit is specific for recognition by their cellular receptor and also confers biological activity[15,53,134,136]. These hormones exert their effects by binding to G protein-coupled surface receptors, called the LH receptor (LH-R) and the FSH receptor (FSH-R)[134,137,138]. Both receptors are mainly expressed in the gonads[139]. In the ovary, LH-R is expressed in theca cells, luteal cells, and interstitial cells, regulating actions such as the synthesis of steroid hormones, ovulation, and the formation of the corpus luteum[139]. In the testicle, LH-R is expressed in Leydig cells, where it stimulates the synthesis of testosterone (T), a precursor hormone of testicular maturation via spermatogenesis.139 LH is related to the manifestation of secondary sexual characteristics in males, and its highest plasma levels are in the spermiation stage. In addition, it intervenes in the capture and incorporation of blood vitellogenin to the oocyte. In the final phase of oocyte maturation, LH levels increase, leading to the production of dihydroxyprogesterone (17α-20β). The 17α-20β is involved in the haploid processes before ovulation and in sodium and potassium transport control[139]. For its part, FSH-R is expressed in the ovary, exclusively in granulosa cells. Its activation by the action of FSH contributes to follicular development and stimulates the synthesis of 17β estradiol. The 17β estradiol acts on the liver to initiate and maintain vitellogenin synthesis in oocytes and is involved in gonadal maturation processes.

Furthermore, FSH induces aromatase expression and thus modulates ovarian estrogen synthesis. On the other hand, in the testis, FSH-R is expressed in Sertoli cells[139]. In trout, plasma FSH increased at the beginning of oogenesis and in the initial phases of spermatogenesis[140]. Also, in Pacific salmon (*Oncorhynchus tshawytscha*), the levels of FSH remained high and declined immediately before ovulation and spermiation. In physiological studies carried out in this same species, FSH-β expression levels increased during the initiation of gonadal growth and decreased in spawning[141]. These results coincide with Schulz *et al.* in 2001[142], where they state that FSH is involved in the initial phases of gametogenesis, and LH mainly regulated the last stages of gonadal maturation. Previous studies have reported that FSH mRNA levels increased while LH mRNA decreased during the transition from female to male in Epinephelus merra. This was associated with testicular development and suggests that FSH could trigger sex change in this species[143]. In recent studies, the expression of LH-β mRNA in the pituitary of carp (*Cyprinus carpio*) increased significantly during the maturation of the male; however, FSH-β mRNA expression did not change significantly during development[136]. As published by Yaron *et al.* in 2003[29], LH-<UNK> and FSH-<UNK> gene expression levels of LH-β and FSH-β were very low in the juvenile stage of carp, while they increased during the ovulation period. In general terms, FSH mainly controls the first stages of spermatogenesis, and LH regulates testicular maturation, ovulation, and spermiation[16,50-52].

Growth hormone (GH)

The growth hormone of teleost fish is a 21-23 kDa protein made up of a single polypeptide chain. Similar to what happens in mammals, GH in fish is produced by somatotropic cells in the anterior region of the pituitary gland[144]. Furthermore, its expression has been confirmed in other fish tissues, including the brain, liver, spleen, and gonads[145,146]. GH is an essential endocrine regulator in many physiological processes in vertebrates. In fish, it is involved in events such as somatic growth, energy metabolism, reproduction, appetite, the function of the immune system, and the regulation of ionic and osmotic balance[147,148]. In addition, it influences aspects of behavior such as aggressiveness and the ability to avoid predators[149]. This hormone is released from the pituitary in response to hypothalamic signals and exerts its effects on target tissues[148,150] binding to the GHR-I and GHRII receptors (hormone receptor growth I and II, respectively)[148,149]. Growth hormone receptors (GHRs) are members of the type I cytokine receptor family[151]. They have been identified in several fish species, such as turbot (*Scopthalmus maximus*)[146], salmon (*Oncorhynchus masou*)[152], and Mozambique tilapia (*Oreochromis mossambicus*)[153]. These receptors are expressed in a wide variety of tissues, including the brain, pituitary, skin, heart, liver, gallbladder, intestine, adipose tissue, kidney, spleen, gonads, and muscle[152-154]. However, the primary expression is in the liver (or hepatopancreas), where GHRs have a significant role in regulating somatic growth[148]. GH binds to its specific receptors in the liver and promotes the release of insulin-like growth factor-I and II (IGF-I and IGF-II), whose primary function is to mediate and increase the growth-promoting function of GH[155]. IGF-I is involved in reproduc-

tion and particularly in mediating the effects of GH on somatic growth[154]. Furthermore, it has been associated with fish metabolism, development, reproduction and osmoregulation[148,150]. In the case of IGF-II, its mRNA has been detected in the liver and the brain, heart, kidney, gills, gastrointestinal tract, pancreatic islets, skeletal muscle, and gonads of fish[150]. This transcript is expressed in juvenile and adult fish, contrary to what has been reported for mammals where its expression occurs only during the early stages of development[156]. GH exerts a lipolytic and anabolic function. The lipolytic action is independent of IGFs and facilitates fats as an energy source in catabolic and malnutrition states[157]. The anabolic action of GH is related to protein metabolism and is mediated by IGFs[157]. The biological functions of IGFs are mediated by binding to specific transmembrane receptors, present in both fish and mammals.

In sexually mature ovaries of Nile tilapia, high levels of mRNA of both GHRs were detected. While in testes of this same species, the highest levels were observed after the stage of sexual maturation[148]. Changes in the expression of IGFs in the gonads and the neuroendocrine regulation of GnRH, GnIH, FSH, LH, GH and the GH / IGF system have been associated with promoting testicular steroidogenesis. They also have a significant influence on the oocyte maturation processes in several species[154,156,158,160]. Taken together, these observations suggest that GH, IGFs, and gonads are closely related and involved in controlling reproductive function.

Prolactin (PRL)

PRL is synthesized mainly by the lactotrophic or PRL-secreting cells found in the pituitary[160,161]. It has a variable length (between 170 and 205 amino acids (aa) depending on the species, with signal peptides of 23-24 aa. Two isoforms have been found in teleosts (PRL188 and PRL177), with different biological activities[83]. Prolactin is generally produced at high levels in pituitary tissues; however, its expression has been evidenced in other tissues such as the liver, intestine, gonads, gills, kidney, spleen, brain, and muscle[162,163]. Plasma PRL levels in Nile tilapia are increased during maternal behavior, suggesting hormonal control[164]. Other studies indicate that PRL mRNA levels and mature protein have been found in the gonads of different fish species, including Mozambique tilapia[167], Nile tilapia[165], goldfish[162,166], and rainbow trout (*Oncorhynchus mykiss*)[166]. This suggests that PRL may be involved in spermatogenesis, vitellogenesis, and ovulation. However, no significant differences were found in PRL mRNA levels during sexual maturation of Japanese eels through *in vitro* studies by Ozaki *et al.* in 2007[168]. According to Onuma *et al.* in 2010[169], in salmon, the levels of PRL mRNA and gonadotropins significantly were increased in the stage of maturation and gonadal development, which suggests that these hormones may be associated with the development of the reproductive system. In addition, PRL levels seem to be involved in many more functions such as developing reproductive cycles, incubation behavior, or feeding the fry[170,171]. It has also been shown to stimulate steroidogenesis in the ovaries and testes and increase their mRNA and plasma levels during sexual maturation in salmonids and tilapia[153,166]. The regulation of PRL synthesis and release into the pituitary is known to be influenced by hypothalamic neurohormones, sex steroids, and plasma factors from other tissues[171]. It is proposed that this hormone can act in an autocrine or paracrine manner and represents an exciting area for future research[171,172].

Thyroid hormones (HTs)

Thyroid hormones (HTs) are involved in various biological events in fish, such as regulating metabolism, growth, development, and reproduction, among others[173-177]. HTs (T3 and T4) are found in two forms in the blood: free and bound to transporter proteins. Less than 1% is in the free form and therefore easily accessible to target cells[178]. The secretion of HTs is under the control of the hypothalamic-pituitary-thyroid axis (Figure 2)[175,177-179]. In the hypothalamus, some neurons synthesize, transport, and release various factors that stimulate or inhibit the release of HTs to the neurohypophysis. Among the stimulatory factors are thyrotropin-releasing hormone (TRH) and the inhibitors Somatostatin and TSH inhibitory factors. Thyroid-stimulating hormone (TSH) is released to the bloodstream, where it reaches the thyroid gland and stimulates the synthesis and release of the two HTs (T3 and T4) into the blood[178,179]. These hormones are lipidic, so they can cross the plasma membrane and reach the cytoplasm. T4 is secreted under normal conditions, while T3, known as the active hormone, is produced mainly from the conversion of T4 to T3. Two enzymes catalyze this process with deiodase activity (DIO1 and DIO2)[180]. T3 crosses the nuclear membrane to interact with its THR α and THR β receptors in the nucleus.

Once the hormone-receptor complex is formed, there is a self-regulation of the expression of the genes (THRα and THR β) that code for the THR α and THR β receptors[177,179]. Some of the first studies in fish was carried out in Pacific salmon, Atlantic salmon (*Salmo salar*), and striped bass (*Morone saxalitis*), where it was evidenced that the thyroid hormones T3 and T4 are transferred from the mother to the egg and are used during the absorption of the yolk sac in the larval period, to later be synthesized by the larva in the exogenous feeding period[181]. In salmon, the increase in plasma T4 levels has been seen in the early stages of gonadal maturation but decreases as vitellogenesis and testicular maturation occur[182]. In stellate sturgeon (*Acipenser stellatus*), high thyroid activity occurs in conjunction with gonadal maturation during preponderance migration and at spawning. In salmonids, the increase in T3 was related to vitellogenesis or the last stages of oocyte development[12,179]. *In vitro* and *in vivo* studies have shown that T3 treatments caused a decrease in LH mRNA levels in goldfish[183,184]. In other trials, T3 administrations in carp increased vitellogenin mRNA (Vtg) levels in the liver, a critical factor in gonadal maturation[185]. However, T3 treatment decreased the expression of estrogen receptors in golden carp testes[176]. In zebrafish, the administration of T3 stimulated the proliferation of Sertoli cells and spermatogonia in the testes[186]. In general, the effects of HTs on reproductive function are species dependent[187,188].

Gonadal development in females and males

Reproductive processes in teleost fish include puberty, spermatogenesis, spawning, and cellular processes such as steroidogenesis[16]. The gonads have the enzymes necessary for the synthesis of steroids and their transformation into a whole series of intermediaries involved in the different phases of reproduction. They produce three types of steroids necessary for reproduction: estrogens or C18 steroids, androgens or C19 steroids, and progestogens or C21 steroids[189]. Gonadal steroids exert their actions on target tissues by binding to specific intracellular receptors since, thanks to their lipophilic nature, they easily penetrate and diffuse within the cell[190,191]. In teleost testes, the synthesis of steroid (androgenic) hormones takes place in Leydig cells. Testosterone (T) is mainly synthesized and, to a lesser extent, 17α-hydroxy-4-pregnen-3-one (DHT), Androstenedione, and 11-ketotestosterone (11-KT)[192]. T is es-

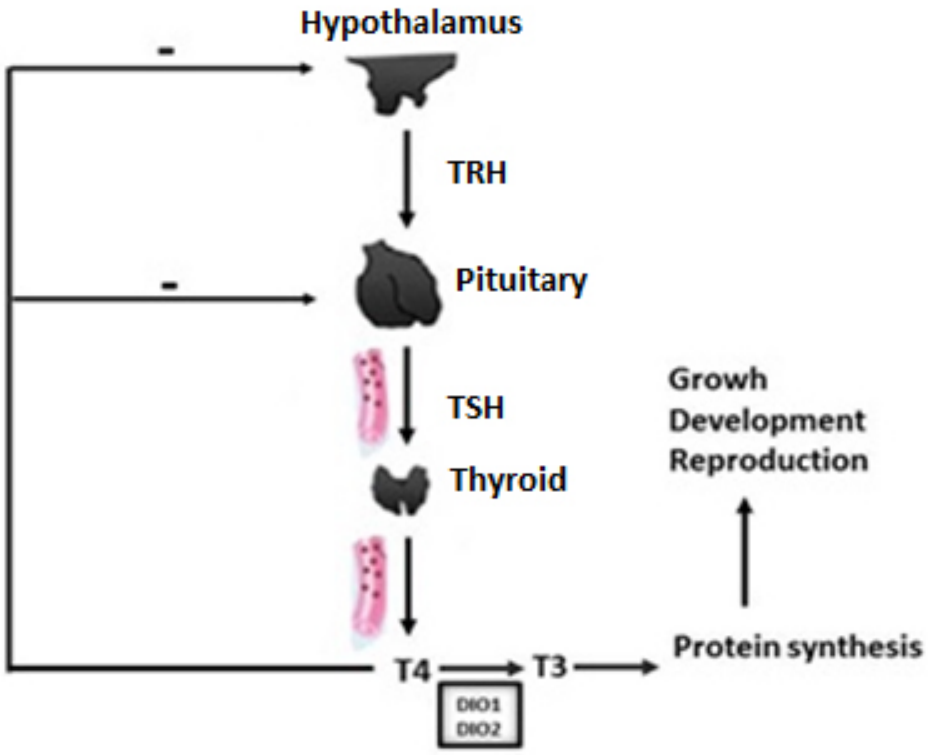

Figure 2. Hypothalamic-Pituitary-Thyroid Axis (HPT). Thyrotropin Releasing Hormone (TRH); Thyroid-stimulating hormone (TSH); Triiodothyronine (T3); Tetraiodothyronine (T4); Enzymes with deiodinase activity (DIO1 and DIO2).

sential in the spermatogenic process and has great importance in female reproductive processes since it acts as a precursor of estrogen biosynthesis. 11-KT is a critical factor in the maturation of gametes, the development of secondary sexual characteristics, and reproductive behavior[193-196]. Spermatogenesis depends on the action of gonadotropins, and their binding mediates this function to their receptors in the gonads. Once this union occurs, the synthesis and secretion route of different sex steroids is activated[197].

In oogenesis, hormones of a steroid and peptide nature are synthesized, which are essential for regulating the reproductive axis in females[53]. The oocyte maturation process occurs within the ovarian follicles and is produced mainly 17β-estradiol (E_2). According to Nagahama and Yamashita in 2008[198], in teleost fish, there are three essential regulators of oocyte maturation: Gonadotropins, maturation inducing hormone (MIH), and maturation promoting factor (MPF). Before oocyte maturation, a change in the steroidogenic pathway from E_2 to DHP occurs in ovarian follicles[199]. This change during ovarian development is regulated mainly by changes in the availability of steroidogenic enzymes[198]. MIH activates MPF and triggers a series of changes associated with oocyte maturation.

One of the most critical processes for the maturation of the oocyte is vitellogenesis. Its principal function is the sequestration and packaging of vitellogenin (Vtg) and the absorption of very-low-density lipoproteins[200,201]. Vtg is synthesized in the liver and is specific to maturing females (Devlin and Nagahama, 2002). The growing ovarian follicles selectively sequester this through specific receptors (VtgRs) that give rise to the formation of Vtg-coated vesicles[202]. Vesicles fuse with lysosomes leads to the formation of multivesicular bodies (MVB). During vitellogenesis, gonadotropins stimulate the production of Testosterone (T) by theca cells, and subsequently, it is aromatized to 17-β estradiol (E_2) in the granulosa cells of the ovarian follicle. In response to this stimulation, plasma E_2 levels increase, which stimulates the production of Vtg in the liver, which is recognized by VtgR and incorporated by the oocyte through micropinocytosis (Figure 3)[1,27]. At the end of vitellogenesis, plasma LH levels increase, and in turn, E2 levels decrease. This results in a transient increase in plasma levels of T and maturation-inducing steroids (MIS), which act at the follicular layers' level to induce the oocyte's final maturation[1]. After the rupture of the follicle, the oocyte is released, in a process called ovulation[196]. Once ovulation occurs, follicular cells undergo morphological changes that lead to the secretion of progesterone (P) and E_2[190,203]. In general, both vitellogenesis and the final maturation of the oocyte are crucial events in the reproductive physiology of females.

Another group of steroid hormones such as corticosteroids, which are usually related to stress, play an essential regulatory role in other physiological processes[196]. In teleost fish, corticosteroids are mainly synthesized in the inter-renal tissue, specifically the head kidney. Plasma corticosteroid concentrations in fish depend on species, sex, and reproductive status[204]. Plasma levels of corticosteroids vary significantly throughout the reproductive cycle. For both females and males, some species contain high cortisol levels in plasma during the pre-spawning period, such as the rainbow trout[205], perch (*Perca fluviatilis*)[206], and masu salmon[207]. In general, steroid hormones play a fundamental role in controlling the reproductive function of teleost fish. These present direct or feedback effects through different hormonal cascades on reproductive functions in fish and constitute critical factors in the regulation of the HPG axis[196]. The gonadal maturation process in fish is highly complex since it includes the production, maturation, release of gametes, synthesis of hormones, and sexual behavior, which requires a large amount of available energy[208]. Although the role of energy in sexual maturation and reproduction has been evidenced. There are still gaps in the knowledge about the influence of metabolic and nutritional status on the regulation of gonadal function in fish[16].

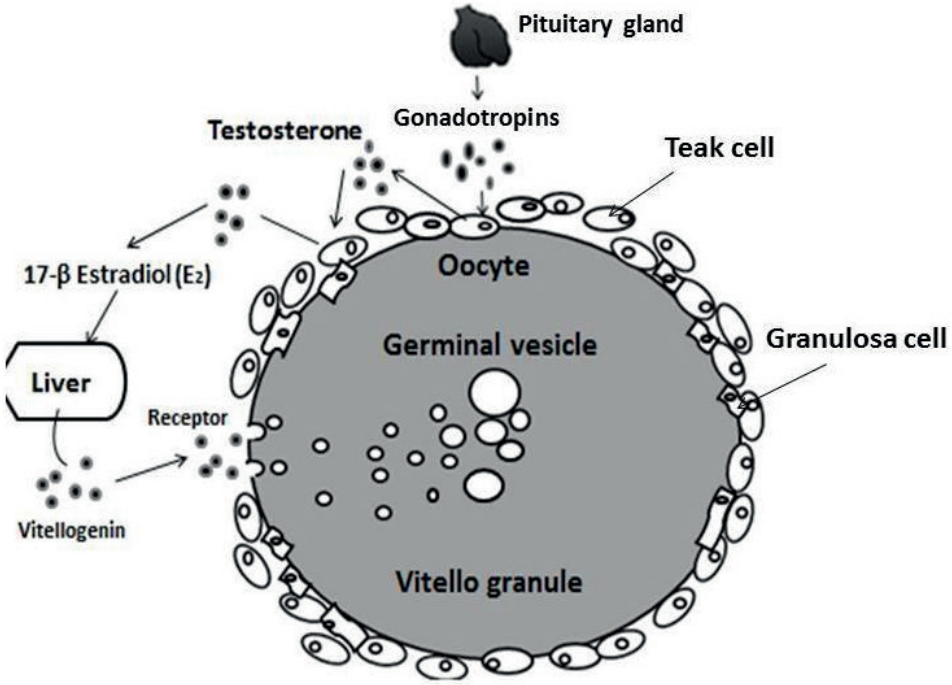

Figure 3. Hormonal regulation of vitellogenesis in teleost fish.

Conclusions

In this review, the fundamental aspects involved in controlling the reproductive function of teleost fish were addressed. The role of hormonal and neuroendocrine regulation of these species is described, which guarantees the proper functioning of the physiological machinery in reproductive events. The hypothalamic and pituitary hormones involved in reproduction in fish point to the immense complexity of endocrine regulation of reproductive processes. A brief overview of the integrative role of some neuropeptides in the regulation of feeding, metabolism, growth, and reproduction was also shown. However, especially in fish, knowledge about these integrative functions of regulatory peptides is not well studied.

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