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Neuroendocrine regulation of somatic growth in fishes

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Growth is a polygenic trait that is under the influence of multiple physiological pathways regulating energy metabolism and muscle growth. Among the possible growth-regulating pathways in vertebrates, components of the somatotropic axis are thought to have the greatest influence. There is growing body of literature focusing on the somatotropic axis and its role regulating growth in fish. This includes research into growth hormone, upstream hypothalamic hormones, insulin-like growth factors, and downstream signaling molecules. Many of these signals have both somatic effects stimulating the growth of tissues and metabolic effects that play a role in nutrient metabolism. Signals of other endocrine axes exhibit profound effects on the function of the somatotropic axis in vivo. In this review we highlight recent advances in our understanding of the teleost fish endocrine somatotropic axis, including emerging research using genetic modified models. These studies have revealed new aspects and challenges associated with regulation of the important steps of somatic growth.

somatic growth, endocrine regulation, fish

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Somatic growth reflects the balance between food intake and all other physiological activities. It is a polygenic trait that is regulated by several physiological pathways that are responsive to environmental and nutritional status and involved in energy metabolism and reproduction [1]. The growth hormone-insulin-like growth factor (GH-IGF) sys-tem, normally characterized as two core components of the somatotrophic endocrine axis, plays a major role in coordinating the growth of vertebrates, including fish. Research into the regulation of fish growth has focused on the production and secretion of growth hormone (GH) from the pituitary. However, the GH-IGF system also includes GH binding proteins (GHBP), GH receptors (GHR), IGF binding protein (IGFBP), and IGF receptors (IGFR) [2,3]. The GH-IGF system of fish is particularly interesting and complex because it consists of multiple subtypes of GHRs, IG-FRs, and IGFBPs that arose through gene duplication events associated with the evolution of the teleost lineage [4,5]. Peripheral regulation of the GH-IGF system results from adjustment of the peripheral sensitivity to GH and IGFs, as well as by modulating the bioavailability and actions of GH and IGFs in target cells. These components are widely distributed and they interact to coordinate both growth and a range of other biological processes such as metabolism, osmoregulation, reproduction, behavior, and immunity. A number of chemicals, including hormones such as growth hormone releasing hormone (GHRH), insulin, somatostatin, and sex steroids, and a variety of transcription factors, proteases, and phosphatases, regulate the synthesis and activity of GHRs, GHBPs, IGFRs, and IGFBPs and the synthesis, secretion, and bioavailability of IGFs. Additionally, a number of environmental factors (e.g.,

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nutritional state, photoperiod, stress, and temperature) can have a significant effect on the expression and activity of peripheral components of the GH/IGF system [1,4].

The endocrine regulation of growth and metabolism is interrelated. Many of the endocrine factors involved in the regulation of somatic growth are involved in lipid and protein metabolism, which in turn play a role in nutrient utilization, immune system function, and reproduction. The complex regulation of these system components appears to be both organism- and tissue-specific [6]. This review will synthesize recent work on the somatotropic endocrine axis of fish, including endocrine regulation of pituitary GH and extrapituitary aspects of the GH-IGF system.

1 Components of the endocrine somatotropic axis

1.1 Growth hormone

GH is a pluripotent hormone produced primarily by the pituitary gland in teleosts, as in other vertebrates. In fish, GH transcripts have been identified in a number of tissues other than the pituitary, including the gill, brain, kidney, liver, pyloric caeca, ovary, skeletal muscle, heart, and spleen. This widespread distribution suggests GH has a number of roles in teleosts, including osmoregulation and reproduction [7,8]. Binding of growth hormone to the receptor leads to receptor dimerization and the activation of an intra- and intercellular signal transduction pathway, leading to growth. The Janus kinase/signal transducers and activators of the transcription (JAK/STAT) pathway are thought to be the primary downstream signaling cascade for GH. Two forms of GHRs have been identified in many fish species, and are most abundant in the liver, gonad, kidney, muscle, pituitary and spleen [9].

In 1985, Zhu et al. [10] demonstrated that GH promoted teleost growth using human GH transgenic goldfish. Incorporation of the GH transgene induced a number of direct effects on several tissues, including an increase in IGF-1 and IGF-2 mRNA expression in a range of organs [8,11]. This suggests that IGF-1 and IGF-2 may be the primary downstream mediators of the growth effects of GH, consistent with observations in all other vertebrates. However, the growth enhancing effect of the GH transgene in fish appears to be dependent on the genetic background [12]. Unlike hemizygote GH transgenic fish, homozygote GH-transgenic zebrafish, that have double the levels of the GH transgene, did not exhibit significant enhancement of growth. This is thought to be a result of an increase in the level of negative feedback within the GH pathway, probably inhibited by the signals, such as suppressors of cytokine signaling 1 (socs1) and socs3 [13].

Observations of GH morphants have revealed that GH is not involved in the regulation of growth and development during early life history stages in zebrafish [14]. Decreased somatic growth and increased adipose tissue accumulation have been observed in zebrafish gh1 mutants. However, the expression levels of all IGF transcripts, including IGF-1, 2a, 2b, and 3, remained unchanged in the whole fish *gh1* mutants compared with those in wild-type siblings [15]. These observations highlight the range of roles fish GH plays in the regulation of growth and lipid metabolism. Kuradomi et al. [16] also reported that the muscle hypertrophy resulting from GH over-expression in zebrafish was independent of local IGF-1 expression. Thus, further studies seems to be needed for learning more about the tissue- and stage-specific patterns and effects of IGFs expression in *gh1* null zebrafish. Historical evidence supports the hypothesis that the somatogenic action of GH is mediated by the hepatic generation of endocrine IGF-1, though more recent data demonstrate that GH also has a direct effect on growing tissues. The contribution of GH via the action of IGFs to the regulation of body growth continues to be a subject of controversy.

1.2 Insulin-like growth factors

IGFs are proteins that have high sequence similarity to insulin but with the addition of an extra D-domain [4]. In mammals, IGFs are primarily secreted by the liver following stimulation by GH. IGF-1 expression is essential to achieve maximal growth in mammals, whereas IGF-2 is thought to be a primary growth factor regulating early development. Loss of IGF-1 or IGF-2 in knock-out mice results in significant loss of body weight [17,18], while over-expression of IGF-1 or IGF-2 causes somatic over-growth in mammals [19,20]. The IGFs bind to IGF receptors, insulin receptor, insulin-related receptor, and possibly other receptors. These receptors are expressed in a range of tissue types, suggesting that IGFs have a range of functions. *In vivo*, IGFs are also regulated by a family of proteins known as the IGFBPs. These proteins help to modulate IGF action in complex ways that involve both inhibiting IGF action by preventing binding to the IGF receptors, or promoting PGF action by promoting delivery to the receptor and increasing the stability of IGFs [4].

Most studies of IGFs in fish have focused on identification of the genes or development of assays to measure the levels of IGFs in tissue and plasma. These studies have shown that the structure, regulation, and functions of IGFs are similar between fish and mammals [21]. Liver tissue contains the greatest concentration of IGF-1 mRNA in trout [22] and gill tissue contains the highest abundance of IGF-1 receptor A (IGF-1RA) mRNA [23]. The type I IGF receptor has been identified in several other tissues in adult fish, including brain, liver, gastrointestinal tract, ovaries, and muscle [24]. The tissue production of IGF-1 and the presence of recep-tors in various tissues suggests it has both paracrine and autocrine organ-specific functions in fish.

Treatment of fish with IGF-1 stimulates growth via mi-

togenesis promotion [25]. Genetic over-expression of *igf-1* and *igf-2* causes dorsalization of embryos characterized by an increase in the size of the anterior neural structures [26,27]. Knockdown of *igf-2a* or *igf-2b* results in ventralization of embryos with reduced growth, reduced sizes of eyes, disrupted brain structures, and a disrupted cardiovascular system, with IGF-2b playing a more significant role in development. During gastrulation, IGF-2a and IGF-2b are required for development of anterior neural structures and for regulation of genes critical to dorsal-ventral patterning. As development proceeds, IGF-2a and IGF-2b play anti-apoptotic roles [28]. These observations suggest that fish IGFs play a critical role in neural induction as well as growth regulation. IGF-1 receptors (IGF-1R) are more abundant in fish than the insulin receptor (IR) [29], suggesting that IGF-1 plays a greater role in the regulation of muscle function than does insulin in fish. In contrast to mammals, specific inhibition of IGF-1R signaling results in reduced body size, retarded development, and increased embryonic lethality in teleosts [30]. During the adult stage, the expression of IGF-1Rs in tissue is responsive to environmental factors, including nutritional state and temperature [31]. Studies in a range of fish species have also demonstrated that blood IGFBP levels fluctuate in response to switches between anabolic and catabolic states. Recent work by Duan and colleagues [32–34] has shown that knockdown of IGFBPs in zebrafish has profound effects on the development of multiple tissues during embryonic and early stages. Taken together, these observations demonstrate that fish IGFBPs are expressed in spatially and temporally restricted patterns, and each IGFBP plays a distinct role in regulating developmental processes.

IGF-1 and IGF-2 have dramatic effects on muscle growth, protein synthesis, and myoblast proliferation in fish [35,36]. However, our understanding of IGFs function on the regulation of skeletal muscle growth in teleost fish is based primarily on studies of myogenic cells in vitro [4]. Few studies have evaluated the regulatory roles of teleost IGFs using *in vivo* models. Recently, we created a mylz2: IGF-1 trans-genic crucian carp (*Carassius auratus*) that overexpressed zebrafish IGF-1 in skeletal muscle. We observed significantly enhanced levels of muscle hyperplasia in IGF-1 transgenic fish. Interestingly, however, when IGF-1 transgenic fish were raised in the same tank as control fish, we observed a significant loss in skeletal muscle mass compared with the control fish. Additionally, there was a shift in production of white muscle toward more oxidative red muscle [37,38], together with increased oxygen consumption rates in the IGF-1 transgenic fish. These results provide an excellent in vivo model for a global understanding of the effects of teleost IGF-1 on myogenic cell differentiation and proliferation and energy homeostasis in teleosts. Using this model, we confirmed that IGF-1 has a mitogenic effect on fish skeletal muscle growth and plays a role in the regulation of muscle differentiation. Thus, the overall phenotype of these IGF-1 transgenic fish is influenced by multiple intrinsic factors, such as endocrine/autocrine signals, the flow of nutrients, the rates of metabolic processes, and energy budgets [39].

1.3 Growth hormone-releasing hormone (GHRH)

The existence of a GH-releasing factor in hypothalamic extracts was first observed in the 1960s [40]. However, it was not until 1981 that a neurohormone peptide, with the ability to stimulate GH release, was first isolated from pancreatic tumor tissue of acromegaly patients [41]. Subsequently, this pancreatic hormone was shown to be identical to the hypothalamic neurohormone GHRH [42]. In mammals, GHRH is a 44-aa polypeptide. The primary function of mammalian GHRH is to stimulate GH release from pituitary somatotrophs upon binding to a specific GHRH receptor (GHRH-R) that belongs to the seven-transmembrane class of G-protein coupled receptors (GPCRs). Additionally, mammalian GHRH exhibits multiple extrapituitary functions, such as cell proliferation activation, sleep cycle regulation, cell differentiation regulation, and promotion of wound healing [43]. The first fish cDNAs encoding GHRH were identified in 2007 in both zebrafish and goldfish. The 27-aa fish GHRH mature peptides exhibit 81.5% homology with human GHRH [44]. Until recently, the GHRH/GHRH-R system has only been documented in a few teleostean species, including zebrafish, goldfish, olive flounder, *Fugu*, medaka, rainbow trout, half-smooth tongue sole, and orange-spotted grouper [44–47]. These fish *ghrhs* are expressed at high levels in the hypothalamus, telencephalon, spinal cord, and at a relative low level in the ovary. Similarly, their specific receptors, *ghrh-rs*, are abundant in the hypothalamus, telencephalon, spinal cord, diencephalon, and pituitary, but only present at low levels in the ovary [44,47]. Based on our recent pituitary transcriptome studies, the levels of both *ghrh* and *ghrh-r* expression were less than 1 RPKM in the zebrafish pituitary at both 45 and 90 d post-fertilization (dpf) [48]. Both *ghrh* and *ghrh-r* are expressed in the head region of zebrafish during the embryonic stage. Functional studies indicate that teleostean GHRH plays a role in stimulating GH release, immunity regulation, and sexual growth dimorphism. GHRH-induced stimulation of GH secretion in fish is mediated by both the adenylate cyclase/cAMP/ protein kinase A pathway and the nitric oxide/nitric oxide synthase pathway [44–47,49]. Inhibition of GHRH translation during embryonic stages by morpholino oligo (MO) did not result in any obvious developmental defects or effects on zebrafish *gh* expression patterns (our unpublished data). Recently, a 66-bp deletion in the 5′-flanking region of largemouth bass GHRH gene was associated with recessive embryonic lethality. However, the levels of *ghrh* and *gh* expression were not reported in the null mutant largemouth bass [50]. Because of its role in the regulation of GH release, there is interest in understanding

the factors controlling GHRH expression. Unfortunately, little is known about the regulation of GHRH expression. In mammals, substance P (a member of the tachykinins family) and clonidine (an α2-adrenergic agonist) have been shown to induce GHRH expression [51,52]. The immune-related induction of GHRH expression has been reported in orange-spotted grouper (*Epinephelus coioides*) and olive flounder (*Paralichthys olivaceus*) following Chitinase and *Edwardsiella tarda* infection, respectively [45,53].

1.4 Pituitary adenylate cyclase-activating polypeptide (PACAP)

PACAP was first identified from the ovine hypothalamus as a factor with the ability to stimulate cAMP formation in rat anterior pituitary cells [54]. PACAP can stimulate GH, gonadotropin, prolactin (PRL), and somatolactin (SL) secretion in teleosts [55,56]. In mammals, GHRH and PACAP are encoded by separate genes, whereas PACAP-related peptide (PRP) and PACAP are present in the same transcript [57]. The duplicate PRP/PACAPs genes and receptors have been identified in zebrafish [58], rainbow trout [59], and other fish species [5,46]. PACAP and GHRH are highly conserved between fish and humans, suggesting they have evolutionarily important physiological functions. Despite being encoded by the same transcript, the pattern of fish PRP and PACAP conservation differs significantly. There is a high level of variation between the PRPs of different fish species [46]. Like GHRH, PRP and PACAP are also classified as members of the glucagon superfamily [56]. Interestingly, *pacap* mRNA levels are approximately 1000-fold higher than those of GHRH in fish, particularly in brain tissue, but also in other organs. Functional studies have revealed that PACAP plays a pivotal role in all organs or tissues in which this superfamily is expressed [60]. Normally, *pacap* mRNA can be detected at the mid gastrula stage during embryogenesis in fish. Knock-down of PACAP in embryos causes morphological defects in specific brain regions without affecting GH expression patterns during zebrafish adenohypophysis development [61]. Additionally, PACAP is involved in the neuroendocrine control of food intake and acts as an anorexigenic peptide to regulate satiety in fish [62]. PACAP is distributed in a range of tissues in mammals and is involved in the regulation of gut motility, airway dilation, immune response, steroid production, and insulin secretion [55]. However, most of these physiological roles have yet to be documented in fish, with the exception of a role in reproduction [63]. The expression of PACAP in fish is affected by environmental temperature and developmental stage. PACAP levels increase as a result of excessive feeding or refeeding after a period of food-deprivation [64,65]. Conversely, PRP-PACAP expression can be significantly down-regulated by increasing the level of dietary lipids [66]. These observations suggest that PACAP is involved in regulating food intake and somatic growth in fish.

1.5 Growth hormone inhibiting hormone (GHIH, or somatostatin, SST)

Somatostatin (SST) was initially discovered because of its inhibitory effect on GH secretion in the sheep hypothalamus. SST was first isolated as a 14-residue peptide (SST-14), with a disulfide bridge that allows its cyclic structure [67]. Transcription of the SST gene leads to the synthesis of a pre-prohormone of SST (PPSST), which can codify various SST-related peptides. SST1 and SST2 have been characterized in all vertebrates to date. Additional SST genes have also been documented in teleosts, including SST3, SST4, and SST5. Most recently, a SST-6 gene was isolated in zebrafish [68]. The two forms of the mature peptides, SST-14 and SST-28 peptides, can be produced by the processing of PPSST1 in mammals and some teleost fish [69]. SST-14 is predominantly produced in the central nervous system (CNS) as well as in many peripheral organs. SST-28 is synthesized primarily by mucosal epithelial cells along the gastrointestinal tract (GIT). Alternate forms of the SST-14 peptide containing a Pro2 residue (Pro2-SST-14) are derived from PPSST-2 [70]. Other forms of SST peptides are derived from PPSST-3 and PPSST-4 and have also been found in teleost fish [71,72]. All of these mature SST peptides are located at the C-terminal of SST precursors [72]. In mammals, SST inhibits most pituitary hormone secretions, including GH and PRL. Generally, SST has an inhibitory effect on basal and/or GHRH- and ghrelin-stimulated GH release [73]. However, a moderate increase in plasma GH levels and a significant decrease in pituitary GH content have been observed in SST null mice. Despite the changes in plasma and pituitary GH, there is no significant difference in plasma IGF-1 levels and body length between wildtype and SST null mice [74]. Taken together, these observations suggest that, although SST has an important inhibitory effect on GHRH, it plays a less prominent role in maintaining baseline GH secretion in the mouse pituitary. Moreover, low levels of SST can even stimulate GH release from somatotrophs via binding to SST receptor 5 (SSTR5). The concentration-dependent, dual effects of SST on GH release have been reported in primary cultures of pituitary cells from swine and baboons [75,76]. The receptors for SST peptides are classified as Class A G protein-coupled receptors (GPCRs). SST receptors (SSTR) are typically classified as 7 trans-membrane domain (TMD) receptors. Five SSTR subtypes have been identified in most mammals, all of which bind endogenous SST and cortistain. These receptors are ubiquitously and differentially expressed in the SST-producing organs, including the blood vessels, muscle, cartilage, bone, and pituitary. Using gene targeting data, researchers have identified an important neuromodulatory role for SSTR2 in the mouse striatum and metabolic abnormalities in SSTR5 null mice associated with obesity and insulin resistance [77,78].

Exogenous administration of SST-14 reduces basal GH

secretion in goldfish, rainbow trout, tilapia, and Chinook salmon [79–81]. The inhibitory effect of SST-14 on GH secretion was clearly demonstrated in several *in vitro* experiments [82,83]. However, the influence of circulating SST on the control of GH secretion has not been clearly addressed in fish. The regulation of GH by SST may be influenced by developmental stage, feeding, and nutritional state [84,85]. Other research suggests that SSTs are involved in the regulation of growth hormone sensitivity of fish hepatocytes, and can cause a reduction in the levels of GHR expression and IGF-1 biosynthesis and secretion [86,87]. SSTR2 activation is linked to inhibition of pituitary GH release in fish [88]. Additionally, there is an inverse correlation between SST plasma levels and thyroid hormone levels in fish [89]. Recently, we observed mortality prior to 20 dpf as a result of severe developmental defects in SSTR5 null zebrafish that had up-regulated *gh* and prolactin mRNA levels compared with wild-type larva (unpublished data).

1.6 Other neuropeptides and neurotransmitters

The neuroendocrine-regulation of GH is also influenced by a group of neurotransmitters and neuropeptides at the hypothalamic and suprahypothalamic levels. As a result GH secretion is influenced by hypophysiotropic and exogenous and endogenous factors. The complexity of these regulatory networks stems from the abundance of different neurotransmitter and neuropeptide neurons present in the hypothalamus. Therefore, many of the effects are status-dependent (e.g., developmental stage or nutritional status). Decreased levels of serum GH have been reported after intraperitoneal injection of norepinephrine (NE). Additionally, both NE and serotonin (5HT) inhibit GH secretion from goldfish pituitary cells cultured *in vitro* [2]. *In vivo* administration of a glutamate agonist, N-methyl-D-aspartate (NMDA), inhibits GH secretion in goldfish, an effect that is enhanced by estradiol (E2) treatment [90]. However, NMDA also stimulates GH secretion in steroid-primed immature rainbow trout [91,92]. Gamma-aminobutyric acid (GABA) inhibits GH secretion *in vivo* but not *in vitro*, suggesting an indirect action, likely by inhibiting the secretion of hypothalamic factors such as dopamine [93].

Glucocorticoids have no positive effect on GH expression, whereas thyroid hormone and retinoic acid stimulate GH expression in pituitary cells from common carp and Atlantic salmon [94]. Norepinephrine and epinephrine suppress basal GH release from goldfish pituitary cells in a reversible and dose-dependent manner. Salmon gonadotropin-releasing hormone (sGnRH) and dopamine, two known GH-releasing factors in fish, stimulate GH release from goldfish pituitary cells and their GH-releasing actions are inhibited by simultaneous treatment with norepinephrine. This effect, however, is not altered by the beta agonist iso-proterenol and α1 agonist methoxamine [95].

Sex steroids also modulate the expression of the core components of the somatotropic axis. Intrapituitary regulators, including gonadotropin and inhibin/activin, provide autocrine/paracrine control over GH synthesis and secretion [96]. In rainbow trout, estrogen treatment significantly reduces food conversion, body growth, and the expression of GHRs, IGFs, and IGFRs [97]. At the somatotroph level, receptor expression of a multitude of neuroendocrine factors integrates the signals from various regulators [96]. Ghrelin was first identified and characterized from the rat stomach as an endogenous ligand of the growth hormone secretagogue receptor. Ghrelin is essential for initiation of *gh* expression in the zebrafish adenohypophysis [98]. Both forms of GHSHR-1a and -1b are found in the pituitary of tilapia. Intraperitoneal injections of Ghrelin significantly increase plasma GH levels and hepatic expression of *ifg-1* and *ghr* in tilapia [99]. Hepatic expression of coho salmon *igf-2* can also be regulated by metabolic hormones, such as insulin, dexamethasone, glucagon, and triiodothyronine (T3) [100]. The expression of *igf-1* in cultured hepatocytes of silver sea bream is significantly increased by incubation with T4, but not T3. Conversely, the expression of *ifg-1* is significantly decreased in hepatocytes in a dose-dependent manner by incubation with cortisol (1–1000 ng mL^{-1}) [101].

2 Balance between of somatic growth and metabolism

GH or IGF-1 overexpression increases skeletal myocyte mitogenesis and consequently increases the metabolic rate in fishes and elevates levels of oxygen consumption [39,102]. The elevation of GH levels in GH-transgenic common carp may influence food intake and feeding behavior by up-regulating the hypothalamic orexigenic factor, agouti-related peptide 1 [103]. Oxygen uptake by GH transgenic common carp fish increases as a result of feeding, not because of an increase in basal metabolism [104]. The elevated basal levels of oxygen consumption during IGF-1 overexpression in crucian carp may result from hyperplasia and cellular changes in the skeletal muscle [39].

In yearling coho salmon subject to different feeding regimes, basal levels of insulin are relatively constant after various periods of fasting, whereas those of IGF-I, IGFBPs, and GH changed in proportion to the duration of the fast. A single meal causes rapid increased but moderate levels of IGF-I 2 h after the meal, but only in the regularly fed fish. GH levels decreased after the meal to the same extent among groups regardless of the fasting period. Thus, the basal levels of IGF-I adjust to the long-term nutritional status and are less responsive to acute nutritional input. IGFBPs maintain their sensitivity to food intake, even after prolonged fasting, suggesting they play a critical role in the nutritional regulation of salmon growth [105]. In the fine flounder, a flatfish with remarkably slow growth, plasma GH levels remain stable and relatively high in comparison

with other teleost species. Plasma GH levels are significantly elevated by 2-weeks fasting. At the onset of refeeding, plasma GH levels decline following a single meal. Thus, plasma GH levels in the fine flounder are strongly linked to nutritional status [106]. In contrast to the direct effects of GH on growing tissues, the systemic effects mediated by hepatic IGFs are influenced by environmental and nutritional status. Both insulin and thyroid hormones are also significantly affected by nutritional status, and both these hormones are required for correct expression of hepatic GHR and GH-signal transduction. This also appears to be the case in fish, as insulin potentiates the in vitro stimulatory action of GH on IGF-1 transcription [107].

In addition to growth promotion, GH also regulates lipid mobilization. During periods of food deprivation, growth is inhibited by lipid depletion. Fasting of rainbow trout for 2 or 6 weeks results in reduced growth and elevated plasma GH. Sensitivity to GH in the liver is also reduced in fasting fish and is associated with reduced levels of *ghr1* and *ghr2* transcripts. However, the sensitivity to GH in adipose tissue increases in fasting fish that exhibit lipid depletion [108]. The sizes of fat deposits are significantly increased in *gh* mutants relative to wild type zebrafish. These observations suggest that GH1 signaling restricts adipose tissue hypertrophy in zebrafish. Lastly, nutrient deprivation of *gh* mutants is associated with decreased adipose tissue mobilization during caloric restriction, further implicating the role of GH1 signaling in maintaining adipose tissue homeostasis [15].

Research conducted primarily in salmonids suggests that GH plays a critical role in seawater adaption as there is a clear correlation between elevated GH and growth and iso-osmotic salinity exposure. Changes in water temperature modulate fish GH, levels being highest during the warmer seasons of the year. Environmental pollutants, including xenoestrogens and heavy metals, also affect GH mediated mechanisms in fish, possibly via interference with the GH receptor and/or GH transcription. Additionally, common stressors in aquaculture such as handling, confinement/overcrowding, and nutritional stress also affect GH levels [109].

3 Interaction between the endocrine regulations on somatic growth and reproduction

Sexual maturation and decreased somatic growth are associated with adolescent development, a process that is controlled by the interconnected neuroendocrine regulatory pathways of the endogenous endocrine system. However, the crosstalk between the networks involved in the somatotrophic endocrine axis and reproductive axis is complex. For example, GHR is expressed in fish gonadal tissue [110] and potentiates the vitellogenesis stimulating effect in eel primary hepatocytes [111]. GH also stimulates E2 synthesis by ovarian tissue in killifish (*Fundulus heteroclitus*) [112] and spotted seatrout (*Cynoscion nebulosus*) [113]. IGFs are also expressed in the testis and ovary of several fish species [114–116]. IGF-1 and/or IGF-2 may serve as paracrine/autocrine regulators of fish spermatogenesis in the testis, and promote proliferation and oocyte maturation in the ovaries [116–118]. The function of gonadal IGF-3 may be limited to the male gonads. The GH-responsiveness of gonadal IGF-1 and IGF-2 is dependent on gonad developmental stage. The gonadal expression of *igf-3* is not regulated by GH signals, but by estrogen and/or gonadotropin [116,119]. IGFR1b is essential for zebrafish primordial germ cell (PGCs) migration and survival [120]. However, estrogen can disrupt post-embryonic growth by reducing GH sensitivity, IGF production, and IGF sensitivity in rainbow trout juveniles [121]. In tilapia, E2 stimulates vitellogenin production primarily by activation of ERα and down-regulation of the GH/IGF-I axis, thus shifting energy from somatic growth towards vitellogenesis at the level of the liver [122]. Dead end (DND) is an RNA-binding protein for that is essential to the survival zebrafish of PGCs. Loss of DND results in PGC-null zebrafish developing into infertile males [123]. In our laboratory, we observed a 25% increase in the body weight of PGC-null *dnd* morphants at 5 months of age compared with male sibling wildtype control zebrafish (unpublished data, Figure 1). This demonstrates the balance between the networks regulating somatic growth and reproduction

Analysis of the global gene expression patterns in the zebrafish pituitary during the juvenile and sex maturation stages revealed that luteinizing hormone β (lhb) is the only pituitary hormone transcript to exhibit a significant change in expression between 45 and 90 dpf [48]. A decrease in spermatic parameters and reproductive success has been observed in GH overexpressing zebrafish males [124]. Additionally, GH overexpression in grass carp (*Ctenopharyngodon idellus*) females is associated with delayed gonadal development, and is accompanied by elevated GH and decreased LH levels in serum [103]. These results from *in vivo* models clearly highlight the regulatory balancing of energy metabolism between the fish endocrine axes for somatic growth and reproduction.

The rate of somatic growth in fish is the primary trait of interest for the majority of aquaculture selection programs. As a result, there has been considerable research into understanding the factors influencing growth in fish. This body of research suggests that the processes controlling somatic growth are a consequence of the species-specific evolutionary processes. Being a polygenic trait, somatogenesis in fish is influenced by appetite, nutrient absorption, metabolism, developmental stage, social behavior, and environmental factors. Although, individual genes can contribute disproportionately to the production traits of an aquaculture species, increased growth can not necessarily be achieved by manipulation of single genes. Teleosts are the largest group

Figure 1 Increased body weight of germ cell depleted zebrafish. The primordial germ cells (PGCs) of zebrafish were impaired at the embryonic stage by injection of dead end (dnd)-specific morpholino oligo (MO). The zebrafish morphants injected with control MO or dnd-MO were raised in the same tank until 5 months post-fertilization (mpf). There was a 24.5% increase in body weight in *dnd*-MO males (0.4956±0.391 g, n=9) compared with the control MO males (0.3980±0.0333 g, n=10) (P<0.01).

of vertebrates with species that occupy a wide range of habitats. Given this, they likely have a range of growth traits and regulatory mechanisms. However, endocrinological studies of somatic growth in fish are in their infancy relative to those in mammals. Additionally, the limited studies to date have used a range of species so it is difficult to draw general conclusions. To increase our understanding of somatic growth and regulation in fish, researchers are increasingly relying on genomic data and using model organisms like zebrafish.

For many years, zebrafish have served as an important tool for understanding vertebrate development and modeling of diseases. In recently years, the species has also emerged as a highly useful teleost model for studying endocrine changes induced by gene targeting techniques, such as transcription activator-like effector nucleases (TALENs) and CRISPR (clustered regularly interspaced short palindromic repeats)/Cas9(CRISPR-associated system Cas 9) [125]. However, it is difficult to perform many classical endocrine assays with the zebrafish model because of its small body size, limited numbers of zebrafish cell lines, and lack of specific antibodies against zebrafish endocrine signals. As the use of zebrafish models increases, it is anticipated that these issues will be addressed. Given the large number of teleosts species that have evolved over millions of years, zebrafish will not provide insights for all teleost species. Additionally, given the increasing importance of aquaculture as a means of providing cheap protein, research may also need to focus on the principle aquaculture species.

The goal of the present review was to highlight recent advances in our understanding of the neuroendocrine regulation of somatic growth. We have provided a simplified illustration of the integrating networks within the endocrine somatotropic and reproductive axes in fish (Figure 2). In doing so, areas that require more attention can be easily identified. Despite the vast body of knowledge that exists documenting endocrine regulation of somatic growth of fish, the mode of GH/IGFs action and the interactions with the hypothalamus-pituitary-gonad (HPG) axis remain poorly understood. Generally, little is known about the actions of the GH/IGF axis on skeletal and gonadal tissue. The classic view posits that hepatic IGF-1 mediates the physiological function of GH secreted from the pituitary. The regulatory functions of SST on GH secretion, ghrelin, and PACAP have been observed in vitro in a range of teleosts. However, recent observations utilizing genetic models generated with gene targeting techniques have been unable to confirm these observations *in vivo*. Research into the temporal and spatial expression of the components of the endocrine somatotropic axis and their actions in stage- and tissue-dependent manners will hopefully help explain the mechanisms. Additionally, very little is known about signaling mechanisms for

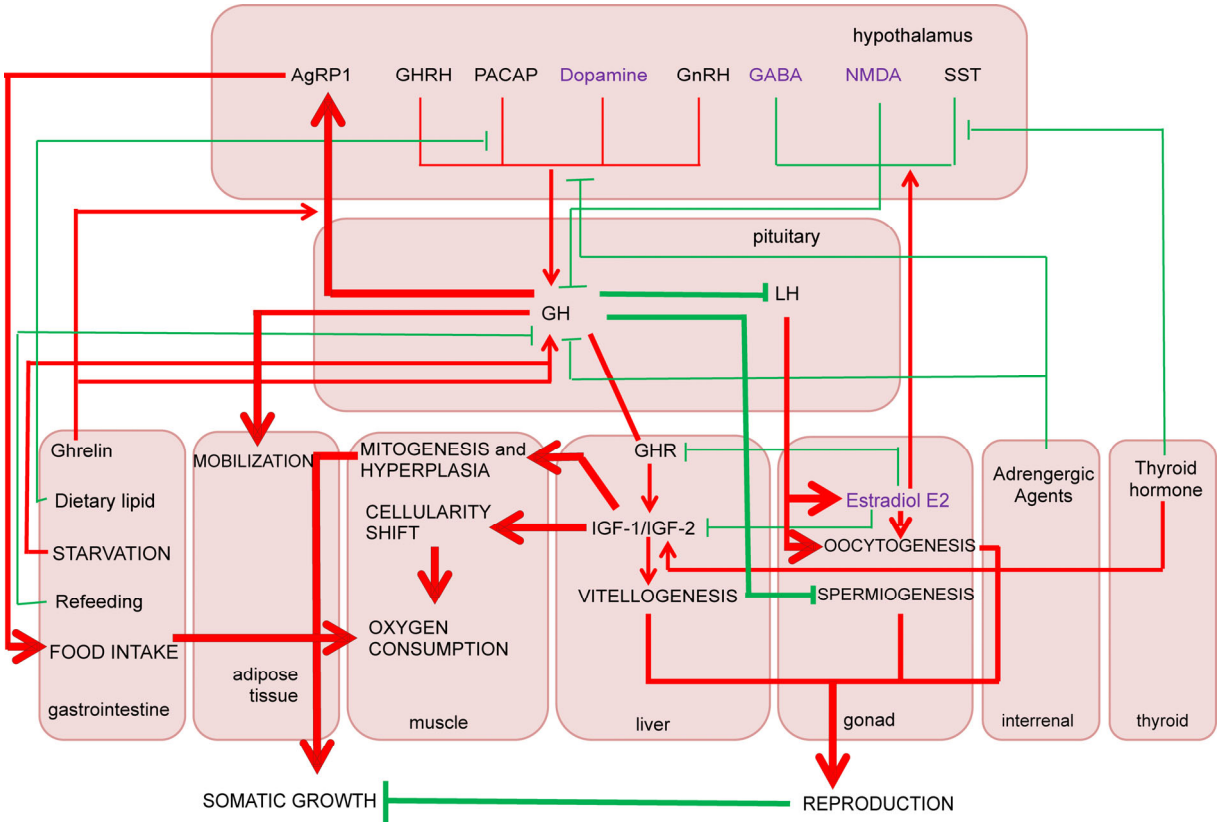

Figure 2 Simplified illustration of the integrating networks of the endocrine somatotropic axis and other endocrine axes in fish. Important protein signals, reagents, and activities are represented by black, purple, and dark blue characters, respectively. Thin lines indicate the conclusions based on *in vitro* work or observation following reagent administration. Thick lines indicate the conclusions drawn on studies with *in vivo* models. Red arrows represent positive regulation. Green bars represent negative regulation. See more details in text.

crosstalk between the endocrine regulatory signaling path-ways of somatic growth and immune responses. Understanding the relationship between somatic growth and other physiological processes is of considerable importance to the development of the aquaculture industry. This understanding is reliant on increased knowledge of the biology of the endocrine somatotropic axis in fish.

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