Fish Physiology and Biochemistry **27:** 217–226, 2002.

The role of somatostatins in the regulation of growth in fish

N.M. Very and M.A. Sheridan*
*Department of Biological Sciences, North Dakota State University, Fargo, ND 58105, USA; *Author for correspondence (Phone: 701-231-8110; Fax: 701-231-7149; E-mail: mark.sheridan@ndsu.nodak.edu)*

Accepted: 15 November 2003

Key words: insulin-like growth factors, growth hormone, growth regulation, somatostatins

Abstract

Somatostatins (SS) are a structurally diverse family of peptide hormones that affect various aspects of growth, development and metabolism in vertebrates. Fish have proved to be useful models for understanding the role(s) of SS in the regulation of growth. Organismal growth is inhibited by SS and fish with impaired growth (caused by fasting or premature transfer to seawater of anadromous species) display enhanced SS production and elevated plasma levels of the hormone. Somatostatins modulate growth at the level of the pituitary through the inhibition of growth hormone (GH) synthesis and secretion. There are, however, significant structure-function relationships with regard to GH inhibition. For example, while SS-14 is a potent inhibitor of GH secretion, catfish SS-22 and salmonid SS-25 appear not to have GH secretotropic effects. Somatostatins also have extra-pituitary effects on growth. For example, SS reduce GH binding capacity and inhibit IGF-I mRNA expression in the liver. In addition, SS inhibit insulin, another factor essential to organismal growth. Finally, SS interact with a variety of reproductive and metabolic processes – actions which suggest that SS help modulate energy partitioning among biological processes.

Introduction

Growth integrates a large number of biological processes to allow a fertilized egg to develop into an adult. The adult structures must then be maintained and modulated appropriate to their function. Animal growth is influenced by genetic, environmental and nutritional factors. For poikilothermic vertebrates such as teleost fish, extrinsic factors are particularly important because many developmental processes of the organisms are dependant on temperature, photoperiod, and food availability (McLean and Donaldson 1993). Integration of internal and external cues and the coordination of organismal growth involves numerous chemical mediators, including growth hormone (GH), insulin (INS), and thyroid hormones (Harvey 1993; Duan 1998).

A central component of growth coordination is the GH-insulin-like growth factor-I (IGF-I) axis. Increasing evidence indicates that many of the growth promoting actions of GH are mediated by IGF-I (McLean and Donaldson 1993; Moriyama et al. 2000). The GH-IGF-I axis begins with GH production in the pituitary gland under the control of multiple hypothalamic hormones, including somatostatins (SS). Growth hormone circulates through the blood, binds to its receptors, and stimulates IGF-I synthesis and secretion from liver and other sites. Insulin-like growth factor binding proteins bind IGFs, transporting them through the blood and modulating their action (Moriyama et al. 2000). Insulin-like growth factor-I evokes biological responses through an IGF-I receptor that is distinct from the INS receptor (Planas et al. 2000). In rainbow trout (*Oncorhynchus mykiss*), IGF-I receptors are present in most tissues, with the receptor mRNAs being most abundant in adult heart and pyloric caeca (Greene and Chen 1999). The complexity of the GH-IGF-I axis has been expanded by several additional observations. Two different forms of GH occur in some teleosts, including rainbow trout and sockeye salmon (*Oncorhynchus nerka*); the forms display 94% identity at the peptide level in rainbow trout, and no

evidence has yet been presented to indicate differential function (Melamed et al. 1998). In addition, GH 'binding proteins', the role of which has not been fully established, have been described in mammals and fish (Sohm et al. 1998; Zhang and Marchant 1999).

Considerable research in mammals and fish has focused on the modulation of growth at the level of pituitary GH synthesis and secretion (Harvey 1993). Given the complexity of the GH-IGF-I axis and a heightened understanding of the SS signaling system, it is becoming increasingly clear that the regulation of growth in fish occurs at many levels (Sheridan et al. 2000). This review will examine the role(s) of SS in the regulation of growth and describe interactions between growth and metabolism as well as between growth and reproduction.

Somatostatin heterogeneity

Somatostatins are a diverse family of peptide hormones that affect many aspects of animal growth, development, and metabolism (Sheridan et al. 2000). The first SS was isolated from ovine hypothalamus and found to inhibit the release of GH from the pituitary of mammals – the action for which the hormone was named (Brazeau et al. 1973). Since its initial discovery, SS peptides ranging in length from 14 (SS-14) to 37 amino acids, depending on species, have been isolated from a wide array of tissues, including the central and peripheral nervous systems, the gastrointestinal tract, pancreatic islets, and other tissues (Patel 1999; Conlon et al. 1997; Sheridan et al. 2000; Lin and Peter 2001).

The molecular heterogeneity of the SS family is the result of tissue-specific differential processing of a SS precursor molecule and of the existence of multiple precursors derived from different SS genes. For example, it is now known that mammals possess not only SS-14, but a 28 amino acid form of SS (SS-28), which result from differential processing of a single precursor, preprosomatostatin I (PPSS I), that contains SS-14 at its C-terminus. The tetradecapeptide has been found in most species so far examined, from hagfish (*Myxine glutinosa*) to humans, suggesting that PPSS I is well conserved among vertebrates (Sheridan et al. 2000). Recently, a SS-like peptide, cortistatin (CST), was cloned in humans, mice and rats (de Lecea et al. 1996; de Lecea et al. 1997). Cleavage of preprocortistatin can potentially yield both long and short forms of CST, of which the 14 amino acid short form in rats is identical to SS-14 at 11 of its 14 amino acids and is able to bind to SS receptors (Fukusumi et al. 1997).

Numerous teleost fish, lampreys and frogs possess PPSSs in addition to PPSS I. Several teleost fish have been shown to possess peptides derived from a second precursor, PPSS II, which contains [Tyr^7, Gly^{10}]-SS-14 at the C-terminus (Sheridan et al. 2000). Rainbow trout express two distinct mRNAs that encode PPSS IIs: PPSS II' and PPSS II" (Moore et al. 1999). Based on the presence of putative processing sites, PPSS II' could yield [Tyr^7, Gly^{10}]-SS-14 as well as an N-terminally extended 28-amino acid peptide; whereas, PPSSII" could yield [Tyr^7, Gly^{10}]-SS-14 in addition to salmonid SS-25 (sSS-25) (Sheridan et al. 2000). Goldfish (*Carassius auratus*) also possesses two different PPSS IIs: one isolated from the brain that contains [Glu^1, Tyr^7, Gly^{10}]-SS-14 and another from intestine that contains [Tyr^7, Gly^{10}]-SS-14 (Lin et al. 2000). A handful of fish species including sturgeon (*Acipenser gueldenstaedti*), lungfish (*Protopterus annectens*), goldfish, pufferfish (*Tetraodon nigroviridis*) and zebrafish (*Danio rerio*), possess a [Pro^2]-SS-14 that suggests a third PPSS, PPSS III. Phylogenetic analysis groups the PPSS IIIs with the CST precursors in mammals (Lin et al. 2000; Genbank accession No. AL296478; Devos et al. 2002; Trabucchi et al. 2003).

Increasing information suggests SS operate through an elaborate, multi-faceted signaling system. The presence of multiple receptor subtypes has been demonstrated in mammals and in fish (Patel 1999; Slagter and Sheridan 2004; Lin and Peter 2001). Of the five receptor subtypes (sst1-5) identified in mammals, all bind both SS-14 and SS-28, while sst5 appears to be selective for SS-28 (Patel et al. 1995). The receptors exhibit overlapping yet distinct expression patterns, suggesting a mechanism for tissue-selective responsiveness (Sheridan et al. 2000; Lin and Peter 2001). Interactions between and among the numerous SS signaling molecules and the receptor subtypes, which can be coupled to a variety of different effector pathways, may underlie the multi-functional nature of the SS family. A wide-spread signaling system also may explain how a particular action (e.g., growth regulation) operates at various levels within an organism.

Growth effects of somatostatins

Organismal growth

In fish, the examination of states of altered growth has provided clues to the role(s) of SS in the regulation of growth. Smoltification, which involves a host of developmental events, is necessary for success in the seawater portion of the life of anadromous salmon (Hoar 1988). Normal smoltification is accompanied by elevated plasma levels of numerous hormones such as GH, INS, IGF-I, and thyroxine (T_4), as well as by increased hepatic IGF-I mRNA levels (Duan 1998). Premature transfer of salmon to seawater can result in growth retardation (stunting) accompanied by significant metabolic and hormonal perturbations. In particular, T_4 and INS levels are depressed, while plasma levels of SS are increased (Sheridan et al. 1998). Interestingly, plasma IGF-I levels are depressed in stunts in the face of normal/high GH levels, primarily due to a GH insensitivity resulting from reduced numbers of GH receptors and from depressed IGF-I expression (Duan 1998).

In many species of fish, periods of food deprivation naturally occur during different phases of their life history (e.g., spawning migration; Love 1970). Prolonged fasting can lead to retarded growth (Pesek and Sheridan 1996). Fasting-associated growth retardation is accompanied by changes in many components of the GH-IGF-I axis: serum GH concentration is elevated, while hepatic GH binding, serum IGF-I, and hepatic IGF-I mRNA are decreased (Duan 1998). Plasma levels of INS and glucagon (GLU) change such that the GLU:INS ratio is higher in fasting fish than in fed animals (Sheridan and Mommsen 1991). In addition, fasting modifies the SS signaling system at several levels: plasma levels of SS and the mRNAs encoding SS increase, the patterns of SS receptor mRNA expression are altered, and the number of high affinity hepatic SS-14 binding sites increases (Ehrman et al. 2002; Slagter and Sheridan 2002; Pesek and Sheridan 1996).

Chronic treatment of rainbow trout with SS-14, as delivered by intraperitoneally implanted mini-osmotic pumps, did not affect food intake, but caused a 28% decrease in food conversion (Very et al. 2001). After 14 days of implantation, reduced food conversion was accompanied by significant growth retardation, which was most pronounced in body length (Very et al. 2001). This is consistent with the observation that anti-SS-14 treatment of Chinook salmon (*Oncorhynchus tshawytscha*) promoted fish growth (Mayer et al. 1994). Instantaneous growth, as assessed by [$^{35}SO_4$]-incorporation into gill cartilage, was also reduced in SS-14 injected fish as well as gill cartilage incubated *in vitro* with SS-14 (Very et al. 2001).

The alterations in SS observed during food deprivation and premature seawater transfer in association with *in vivo* effects of the hormone support a role for SS in regulating organismal growth of fish. The mode of SS action, however, may not be tied solely or directly to the inhibition of pituitary GH secretion. This is evidenced by the observation that GH levels can be elevated in the face of elevated SS during both fasting and premature seawater transfer. This observation, which may have numerous explanations [e.g., wide-spread origin of SS (particularly pancreatic) coupled with reduced somatotrope sensitivity to SS], appears somewhat paradoxical at first glance. Such an 'uncoupling', however, would provide a means to retard growth while retaining other GH actions (e.g., catabolic; Sheridan 1994) – effectively separating the growth promoting actions of GH from its metabolic actions – that would be adaptive under nutrient-limiting conditions. Given the multifaceted nature of the SS signaling system that involves significant molecular heterogeneity of many of the signaling elements (ligands, receptors, etc.), the nature of SS role in growth will prove undoubtedly complex and the search will be fraught with challenges.

Pituitary actions

The most studied aspect of SS action is the modulation of GH at the level of the pituitary. Decreases in the plasma levels of GH after treatment with exogenous SS-14 have been shown in rainbow trout, coho salmon (*Oncorhynchus kisutch*), and goldfish (Very et al. 2001; Sweeting and McKeown 1986; Diez et al. 1992; Cook and Peter 1984). In coho salmon, treatment with mammalian SS-25 (SS-25) and SS-28 also decreased plasma GH levels (Diez et al. 1992).

As in mammals, SS-14 does not alter steady-state levels of GH mRNA in either rainbow trout or tilapia (*Oreochromis mossambicus*), suggesting a post-transcriptional role for SS in the regulation of GH by modulation of protein synthesis and secretion (Melamed et al. 1996; Yada and Hirano 1992). *In vitro* studies of GH release from the pituitary of goldfish (Figure 1) have shown that SS-14, mammalian SS-28, and [Pro^2]-SS-14 reduce GH release to approximately the same extent, while goldfish brain SS-28 (gbSS-28)

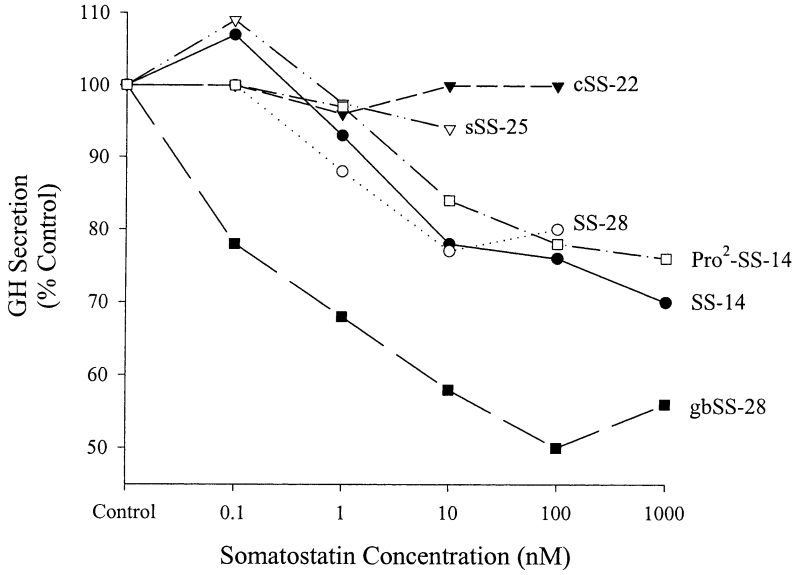

Figure 1. Differential effects of somatostatin isoforms on the release of growth hormone from the pituitary gland *in vitro.* Data derived from studies on goldfish: Marchant et al. 1987; Marchant and Peter 1989; Yunker et al. 2003. Abbreviations: catfish somatostatin-22, cSS-22; salmonid somatostatin-25, sSS-25; mammalian somatostatin-28, SS-28; [Pro^2]-somatostatin-14, Pro^2-SS-14; somatostatin-14, SS-14; goldfish brain somatostatin-28, gbSS-28.

appears to be more effective in reducing GH release (Marchant et al. 1987; Yunker et al. 2003). These results are consistent with results in mammals in which both SS-14 and mammalian SS-28 inhibit GH release (Tannenbaum and Epelbaum 1999).

Neither the [Tyr^7, Gly^{10}]-SS-14-containing sSS-25, nor catfish SS-22 (cSS-22), a unique SS form, affected GH secretion from goldfish pituitaries (Oyama et al. 1980; Marchant et al. 1987; Marchant and Peter 1989).

Structure-function studies carried out in mammals have shown that amino acids 6-11 of SS-14 along with a disulfide bridge are required for the reduced release of GH, although selected substitutions (e.g., D-Trp^8) seem to be permissible (Rivier et al. 1975; Janecka et al. 2001). Catfish SS-22 contains multiple substitutions both within and outside this functional region, which may explain its inability to inhibit GH release (Conlon et al. 1997). In sSS-25, however, the entire 13 amino acid C-terminal region (including the functional region) is the same as in gbSS-28, therefore perhaps implicating the N-terminal region of the peptide in the lack of effectiveness in inhibiting GH release (Sheridan et al. 2000). Another possible explanation for the lack of effect by sSS-25 in goldfish is cross-species differences in the ligand-receptor interaction. To our knowledge, the effect of sSS-25 on GH release in salmonids has not been examined.

A recent study in goldfish showed that the different SS forms are able to differentially trigger various signal transduction pathways in the pituitary. Although SS-14, [Pro^2]-SS-14, and gbSS-28 all suppressed cAMP production, the 28 amino acid form was least effective in terms of cAMP accumulation, even though it caused the greatest decrease in GH release (Yunker et al. 2003). Inwardly rectifying K^+ channels participate in the reduction of GH secretion by gbSS-28, but not by SS-14 or [Pro^2]-SS-14 (Yunker et al. 2003). Goldfish brain SS-28 was also less effective than both SS-14 and [Pro^2]-SS-14 in inhibition of GH release due to activation of Protein Kinase C (Yunker et al. 2003). The physiological significance of these results in goldfish and their relationship to the various SS receptor subtypes remains to be examined. Studies in mammals using receptor subtype-specific agonists have shown that sst2 and sst5 mediate the inhibitory effects of SS on GH secretion (Parmar et al. 1999). A similar function for these receptor subtypes is hypothesized in goldfish pituitary where sst2 and sst5 mRNAs are the most prevalent forms (Lin and Peter 2001; Lin et al. 2002).

In vitro studies using pituitaries have allowed examination of the rebound of GH release following SS removal. After removal of the SS-14 treatment of pituitaries, a recovery in GH to basal levels was not observed in rainbow trout or Chinese grass carp

(*Ctenopharyngodon idellus*) (Agustsson et al. 2000; Wong et al. 1998). In the trout, however, dopamine was able to increase the low levels of GH above basal levels; therefore, a stimulatory action, such as that of dopamine, may be necessary for a reversal of the inhibitory effects of SS (Agustsson et al. 2000). Cultured pituitaries from the turbot (*Psetta maxima*) were only able to respond to stimulation by secretagogues such as forskolin and the phorbol ester, 12-O-tetradecanoylphorbol 13-ester (TPA), in the presence of SS; however, this elevation was still below basal levels (Rousseau et al. 2001).

Although the general model for SS inhibition of GH is comprised of SS production in the hypothalamus and action on the pituitary, other possible mechanisms are emerging and need to be examined. For example, PPSS-I and PPSS-II mRNA, but not PPSS-III, expression were demonstrated in pituitary fragments of the goldfish; therefore, paracrine and autocrine effects of SS-14 also may need to be explored (Yunker et al. 2003).

Extra-pituitary actions

Since their initial discovery, SS have been identified in numerous tissues other than the hypothalamus, including various regions of the central and peripheral nervous systems, pancreas, gut, urogenital tract, muscle, adrenal gland, thyroid and pituitary (Lin et al. 2000; Tannenbaum and Epelbaum 1999). Somatostatin receptors have also been found to be widely expressed, suggesting that SS have extra-pituitary functions (Sheridan et al. 2000). In addition, the presence of a GH mRNA in the intestine was recently demonstrated in coho salmon (Mori and Devlin 1999). Whether SS acts in an endocrine, autocrine, or paracrine fashion to inhibit GH production and secretion in fish tissues other than the pituitary remains to be examined. The possibility that SS have other actions which indirectly or directly affect growth also exists.

Somatostatins may modulate growth through mechanisms other than direct regulation of GH. In rainbow trout, SS have been shown to modulate the GH-IGF-I axis at the level of the liver. Recent data indicate that SS-14 and sSS-25 reduce the number of hepatic GH receptors *in vivo* and *in vitro*, suggesting that SS not only reduces GH levels, but decreases sensitivity to GH (Howe and Sheridan 2002). Intraperitoneal injection of rainbow trout with SS-14 decreased IGF-I levels in the plasma, while also reducing levels of hepatic IGF-I mRNA (Howe et al. 2000). Whether the observed effects on IGF-I are due to direct or indirect control by SS remains to be examined. A direct action of SS is suggested by reduced [^{35}S]-sulfate incorporation into gill cartilage incubated *in vitro* (Very et al. 2001).

Insulin is required for normal growth of fish and INS deficiency results in growth retardation. Streptozotocin injection of coho salmon resulted in decreased organismal growth (Plisetskaya and Duan 1994). Reduction of plasma INS by streptozotocin injection also reduced hepatic IGF-I mRNA (Plisetskaya and Duan 1994). This action of INS appears to be indirect because INS only elevated IGF-I mRNA levels in hepatocytes isolated from coho salmon when co-incubated with GH (Duan et al. 1994). Insulin also acts synergistically with GH to stimulate hepatic IGF-I production and release in mammals and fishes. For example, IGF-I mRNA expression in isolated coho salmon hepatocytes was higher with INS and GH than with GH alone (Duan et al. 1994). Such an effect of INS on IGF-I expression has only been demonstrated in the liver (Duan 1998). The extent to which SS may disrupt INS-mediated growth in fish is still emerging. In rainbow trout, sSS-25 but not SS-14 reduced plasma INS levels within 1 h of injection (Eilertson and Sheridan 1993). In addition, plasma INS levels were depressed in SS-induced growth retarded rainbow trout (Very et al. 2001).

Thyroid hormones also are necessary for normal growth and development of fish (Power et al. 2001). In salmon with hypothyroidism induced by treatment with propylthiouracil, reduced body growth and less efficient food conversion have been shown (Sullivan et al. 1987). Induced hypothyroidism also results in decreased GH secretion in both mammals and coho salmon; although, such an effect in salmon has only been shown during smoltification (Peake et al. 1973; Ebbesson et al. 1998). The role that SS play in the modulation of fish growth through the thyroid axis remains to be fully established. In mammals, SS modulate the thyroid axis by inhibiting synthesis and secretion of thyroid stimulating hormone, a mechanism which may also be present in fish (Patel 1999). A recent study in mature female rainbow trout showed that plasma T_3 and T_4 are inversely correlated with SS-14 levels (Holloway et al. 1999).

Interactions with reproduction and metabolism

Interactions with reproduction

As fish develop, increasing amounts of energy are needed for sexual maturation and reproduction. Energy is provided, in part, by channeling resources away from organismal growth. Fish continue to grow at a much slower rate, while preparation for reproduction accelerates. Sexual maturation is an interesting period in the life histories of fish because anabolic and catabolic processes need to occur at the same time. It is important to note that recent data indicate that the sexual maturation of male and female fish may be modulated differently, at least in part; therefore, it may be necessary to evaluate the two genders independently (Holloway et al. 1999). The involvement of GH in sexual maturation is well established. Growth hormone enhances ovarian maturation and stimulates gonadal steroidogenesis and 17β-estradiol (E_2) enhances GH secretion (Holloway and Leatherland 1998). Sexual maturation is accompanied by elevated plasma levels of GH and E_2 at the same time as reduced plasma SS levels (Holloway et al. 1999).

Elevated levels of E_2 are important in modulating SS actions during sexual maturation. If left unchecked, SS would inhibit the release of GH from the pituitary. 17β-Estradiol implantation of immature rainbow trout results in depressed levels of plasma SS-14 and sSS-25 (after 2 weeks) (Mercure et al. 2001). 17β-estradiol also blocks SS inhibition of GH secretion and affects SS mRNA expression in rainbow trout and goldfish (Holloway et al. 1997; Holloway et al. 2000; Canosa et al. 2002). In rainbow trout, implantation with E_2 decreased both hypothalamic and pancreatic PPSS I mRNA expression, while PPSS II" mRNA expression was only reduced in the hypothalamus (Holloway et al. 2000). Interestingly, implantation of goldfish with E_2 resulted in increased mRNA expression of PPSS I and PPSS III in the forebrain (Canosa et al. 2002). Such disparate results may stem from a species-specific difference in regulation of SS mRNA expression, the use of fish of different maturity (juvenile vs. sexually regressed), or differing modes of E_2 delivery (e.g., coconut oil or solid silicone implant).

In some species of fish, including goldfish, carp (*Cyprinus carpio*) and tilapia, gonadotropin-releasing hormone (GnRH) not only regulates reproduction, but also increases GH secretion from the pituitary (Marchant and Peter 1989; Lin et al. 1993; Melamed et al. 1995). In other species, including catfish (*Ictalurus punctatus*) and eel (*Anguilla anguilla*), no effect of GnRH on GH release is observed (Bosma et al. 1997; Rousseau et al. 1999). In goldfish, SS-14 inhibits GnRH-stimulated GH secretion (Marchant et al. 1989). This supports the idea that modulation of SS is necessary to attain the elevated levels of GH required for normal sexual maturation.

It remains to be examined how reduced somatic growth occurs in the face of the elevated GH levels during sexual maturation. An increase in gonadal growth, however, is observed during maturation, suggesting a tissue-specific action of GH. Perhaps during sexual maturation there is tissue-specific modulation of GH receptors or of IGF-I expression.

Interactions with metabolism

When nutrients become limited, such as during migration or smoltification, energy must be re-allocated away from growth to sustain body functions. Somatostatins may play a role in this shift in energy use through actions at several levels. Somatostatin-inhibited INS release would result in a shift from anabolic processes to catabolic processes (Eilertson and Sheridan 1993; Plisetskaya and Duguay 1993). Insulin deficiency induced by immunoneutralization leads to depletion of stored lipids and carbohydrates (Plisetskaya et al. 1988). Somatostatin deficiency, on the other hand, results in elevated plasma INS levels accompanied by increased glycogenesis and by reduced lipolysis (Plisetskaya et al. 1986; Plisetskaya et al. 1989). Somatostatins also act directly on target cells to mobilize lipid and carbohydrate (Sheridan 1994). Insulin modifies the hepatic sensitivity to SS by decreasing the number of high affinity SS receptors (Pesek et al. 1998). Taken together, these data indicate that the hormonal alterations (e.g., increased SS; reduced INS relative to GLU) that occur during food deprivation underlie the accompanying metabolic adjustments (e.g., increased lipolysis and glycogenolysis; Sheridan and Mommsen 1991; Ehrman et al. 2002). Furthermore, that SS inhibits growth concomitant with its indirect and direct metabolic actions assures appropriate energy allocation when nutrients may be limiting. Similarly, SS may serve to appropriately channel energy reserves during sexual maturation.

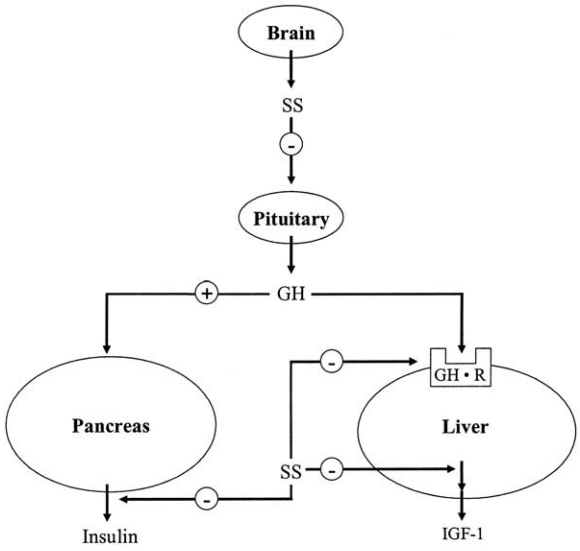

Figure 2. Model of growth regulation in fish. Somatostatins (SS) modulate growth at the level of the pituitary as well as at the liver and pancreas. Growth hormone, GH; growth hormone receptor, GH-R; insulin-like growth factor-I, IGF-I.

Conclusion

Somatostatins are a diverse family of peptide hormones that elicit their effects through a wide-spread, multi-faceted signaling system. Such an elaborate signaling system underlies the vast array of biological responses evoked by the hormone family – several of which embrace aspects of growth (Sheridan et al. 2000). Somatostatins influence organismal growth at many levels (Figure 2). A main influence of SS is on the GH-IGF-I axis at the level of the pituitary gland. Somatostatins directly inhibit GH synthesis and secretion from the pituitary; however, some forms of SS appear to be more potent inhibitors of GH than others and some forms of SS appear, ironically, to be unable to affect GH release, which underscores the importance of structure-function relationships within the SS signaling system. Evidence also is emerging that SS affect the GH-IGF-I axis at the level of the liver. For example, hepatic GH receptor number as well as IGF-I synthesis and secretion may be important targets of regulation. Whether SS affect the extra-pituitary production of GH is not known. Somatostatins also influence other hormonal systems involved with growth, including insulin and potentially thyroid hormones and corticoids, and may serve as a means of integrating these systems with the GH-IGF-I axis for coordinate control of organismal growth. Moreover, because of their involvement in metabolism and reproduction, SS also may serve to coordinate these processes with growth.

Our understanding of the complex mechanisms through which SS modulate growth is only in the beginning stages. Information is slowly emerging regarding many elements of the SS signaling system (e.g., identification of SS receptor subtypes, ligand-binding characteristics of receptor subtypes), but many more studies will be necessary to fully describe the complex system and to understand the biological significance of the complexity. Future studies will need to resolve which SS forms are interacting with which SS receptor subtypes (and associated cellular effector pathways) to play which roles in the regulation of growth. Ultimately, such work will lead to a better understanding of how SS regulate growth in fish and how growth is coordinated with reproduction and metabolism.

Acknowledgements

We are extremely grateful to our past and current collaborators (B.Th. Björnsson, Walton Dickhoff, Alison Holloway, John Leatherland, Steve McCormick, Erika Plisetskaya, and Penny Swanson) for their contributions to this work. We also would like to thank Jeffrey Kittilson for his assistance with the preparation of the manuscript. Some of the research presented in this paper was supported by grants from the National Science Foundation (IBN 0076416) and the US Department of Agriculture (NRICGP 98-35206-6410) to MAS.

References

Agustsson, T., Ebbesson, L.O.E. and Björnsson, B.T. 2000. Dopaminergic innervation of the rainbow trout pituitary and stimulatory effect of dopamine on growth hormone secretion *in vivo*. Comp. Biochem. Physiol. 127A: 355–364.

Bosma, P., Kolk, S., Rebers, F., Lescroart, O., Roelants, I., Willems, P. and Schulz, R. 1997. Gonadotrophs but not somatotrophs carry gonadotropin-releasing hormone receptors: Receptor localization, intracellular calcium, and gonadotropin and GH release. J. Endocrinol. 152: 437–446.

Brazeau, P., Vale, W., Burgus, R., Ling N., Butcher, M., Rivier, J. and Guillemin R. 1973. Hypothalamic polypeptide that inhibits the secretion of immunoreactive pituitary growth hormone. Science 179: 77–79.

Canosa, L.F., Lin, X. and Peter, R.E. 2002. Regulation of expression of somatostatin genes by sex steroid hormones in goldfish forebrain. Neuroendocrinol. 76: 8–17.

Conlon, J.M., Tostivint, H. and Vaudry, H. 1997. Somatostatin- and Urotensin-II-related peptides: molecular diversity and evolutionary perspectives. Regul. Pept. 69: 95–103.

Cook, A.F. and Peter, R.E. 1984. The effects of somatostatin on serum growth hormone levels in the goldfish, *Carassius auratus*. Gen. Comp. Endocrinol. 54: 109–113.

de Lecea, L., Ruiz-Lozano, P., Danielson, P.E., Peelle-Kirley, J., Foye, P.E., Frankel, W.N. and Sutcliffe, J.G. 1997. Cloning, mRNA expression, and chromosomal mapping of mouse and human preprocortistatin. Genomics. 42: 499–506.

de Lecea, L., Criado, J.R., Prospero-Garcia, O., Gautvik, K.M., Schweitzer, P., Danielson, P.E., Dunlop, C.L., Siggins, G.R., Henriksen, S.J. and Sutcliffe, J.G. 1996. A cortical neuropeptide with neuronal depressant and sleep-modulating properties. Nature 381: 242–245.

Devos, N., Deflorian, G., Biemar, F., Bortolussi, M., Martial, J.A., Peers, B. and Argento, F. 2002. Differential expression of two somatostatin genes during zebrafish embryonic development. Mech. Dev. 115: 133–137.

Diez, J.M., Giannico, G., McLean, E. and Donaldson, E.M. 1992. The effects of somatostatins (SRIF-14, 25 and 28), galanin and anti-SRIF on plasma growth hormone levels in coho salmon (*Oncorhynchus kisutch*, Walbaum). J. Fish Biol. 40: 887–893.

Duan, C. 1998. Nutritional and developmental regulation of insulin-like growth factors in fish. J. Nutr. 128: S306–S314.

Duan, C., Duguay, S.J., Swanson, P., Dickhoff, W.W. and Plisetskaya, E.M. 1994. Tissue-specific expression of insulin-like growth factor I mRNAs in salmonids: developmental, hormonal, and nutritional regulation. In: Perspective in Comparative Endocrinology. pp. 365–372. Edited by K.G. Davey, S.S. Tobe and D.E. Peter. National Research Council of Canada, Toronto, Canada.

Ebbesson, L.O.E., Björnsson, B.Th., Stefansson, S.O. and Ekström, P. 1998. Propylthiouracil-induced hypothyroidism in coho salmon, *Oncorhynchus kisutch*: effects on plasma total thyroxine, total triiodothyronine, free thyroxine, and growth hormone. Fish Physiol. Biochem. 19: 305–313.

Eilertson, C.D. and Sheridan, M.A. 1993. Differential effects of somatostatin-14 and somatostatin-25 on carbohydrate and lipid metabolism in rainbow trout *Oncorhynchus mykiss*. Gen. Comp. Endocrinol. 92: 62–70.

Ehrman, M.M., Melroe, G.T., Moore, C.A., Kittilson, J.D. and Sheridan, M.A. 2002. Nutritional regulation of somatostatin expression in rainbow trout, *Oncorhynchus mykiss*. J. Fish Physiol. Biochem. 26:309–314.

Fukusumi, S., Kitada, C., Takekawa S, Kizawa H, Sakamoto J., Miyamoto, M., Hinuma, S., Kitano, K. and Fujino M. 1997. Identification and characterization of a novel human cortistatin-like peptide. Biochem. Biophys. Res. Commun. 232: 157–163.

Greene, M.A. and Chen, T.T. 1999. Characterization of teleost insulin receptor family members. II. Developmental expression of insulin-like growth factor type I receptor messenger RNAs in rainbow trout. Gen. Comp. Endocrinol. 115: 270–281.

Harvey, S. 1993. Growth hormone secretion in poikilotherms and homeotherms. In: The Endocrinology of Growth, Development, and Metabolism in Vertebrates. pp. 151–182. Edited by M.P. Schreibman, C. Scanes and P.K.T. Pang. Academic Press, New York.

Hoar, W.S. 1988. The physiology of smolting salmonids. In: Fish Physiology, V. XIB. pp. 275–343. Edited by W.S. Hoar and D.J. Randall. Academic Press, New York.

Holloway, A.C., Sheridan, M.A. and Leatherland, J.F. 1997. Estradiol inhibits plasma somatostatin 14 (SRIF-14) levels and inhibits the response of somatotrophic cells to SRIF-14 challenge *in vitro* in rainbow trout, *Oncorhynchus mykiss*. Gen. Comp. Endocrinol. 106: 407–414.

Holloway, A.C. and Leatherland, J.F. 1998. Neuroendocrine regulation of growth hormone secretion in teleost fishes with emphasis on the involvement of gonadal sex steroids. Rev. Fish Biol. Fish. 8: 1–21.

Holloway, A.C., Sheridan, M.A., Van Der Kraak, G. and Leatherland, J.F. 1999. Correlation of plasma growth hormone with somatostatin, gonadal steroid hormones and thyroid hormones in rainbow trout during sexual recrudescence. Comp. Biochem. Physiol. 123B: 251–260.

Holloway, A.C., Melroe, G.T., Ehrman, M.M., Reddy, P.K., Sheridan, M.A. and Leatherland J.F. 2000. Effect of 17β-estradiol on the expression of somatostatin genes in rainbow trout, *Oncorhynchus mykiss*. Am. J. Physiol. 279: R389–R393.

Howe, N.M., Knutson, D.L., Kittilson, J.D. and Sheridan, M.A. 2000. *In vivo* effects of somatostatin on the growth hormone-insulin-like growth factor-1 axis of rainbow trout. 4^{th} International Symposium on Fish Endocrinology; Program and Abstracts. Seattle, WA.

Howe, N.M. and Sheridan, M.A. 2002. Somatostatin alters hepatic growth hormone sensitivity in rainbow trout. 84^{th} Annual Meeting of the Endocrine Society; Program and Abstracts. San Francisco, CA. P3-271.

Janecka A, Zubrzycka M, Janecki T. 2001. Somatostatin analogs. J. Pept. Res. 58: 91–107.

Lin, X.W., Lin H.R. and Peter, R.E. 1993. Growth hormone and gonadotropin secretion in the common carp (*Cyprinus carpio* L.). *In vitro* interactions of gonadotropin-releasing hormone, somatostatin and the dopamine agonist apomorphine. Gen. Comp. Endocrinol. 89: 62–71.

Lin, X., Nunn, C., Hoyer, D., Rivier, J. and Peter, R.E. 2002. Identification and characterization of a type five-like somatostatin receptor in goldfish pituitary. Mol. Cell. Endocrinol. 189: 105–116.

Lin, X., Otto, C.J., Cardenas, R. and Peter, R.E. 2000. Somatostatin family of peptides and its receptors in fish. Can. J. Physiol. Pharmacol. 78: 1053–1066.

Lin, X. and Peter, R.E. 2001. Somatostatins and their receptors in fish. Comp. Biochem. Physiol. 129B: 543–550.

Love, R.M. 1970. The Chemical Biology of Fishes. New York: Academic Press.

Marchant, T.A., Chang, J.P., Nahorniak, C.S. and Peter, R.E. 1989. Evidence that gonadotropin-releasing hormone also functions as a growth hormone-releasing factor in the goldfish. Endocrinol. 124: 2509–2518.

Marchant, T.A., Fraser, R.A., Andrews, P.C. and Peter R.E. 1987. The influence of mammalian and teleost somatostatins on the secretion of growth hormone from goldfish (*Carassius auratus* L.) pituitary fragments *in vitro*. Regul. Pept. 17: 41–52.

Marchant, T.A. and Peter R.E. 1989. Hypothalamic peptides influencing growth hormone secretion in the goldfish, *Carrasius auratus*. Fish Physiol. Biochem. 7: 133–139.

Mayer, I., McLean, E., Kieffer, T.J., Souza, L.M. and Donaldson, E.M. 1994. Antisomatostatin-induced growth acceleration in Chinook salmon (*Oncorhynchus tshawytscha*). Fish Physiol. Biochem. 13: 295–300.

McLean, E. and Dondalson, E.M. 1993. The role of growth hormone in the growth of poikilotherms. In: The Endocrinology of Growth, Development, and Metabolism in Vertebrates. pp. 43–71. Edited by M.P. Schreibman, C. Scanes and P.K.T. Pang. Academic Press, New York.

Melamed, P., Eliahu, N., Levavi-Sivan, B., Ofir, M., Farchi-Pisanty, O., Rentier-Delerue, F., Smal, J., Yaron, Z. and Noar, Z. 1995. Hypothalamic and thyroidal regulation of growth hormone in tilapia. Gen. Comp. Endocrinol. 97: 13–30.

Melamed, P., Gur, G., Elizur, A., Rosenfeld, H., Sivan, B., Rentier-Delrue, F. and Yaron, Z. 1996. Differential effects of gonadotropin-releasing hormone, dopamine and somatostatin and their second messengers on the mRNA levels of gonadotropin IIβ subunit and growth hormone in the teleost fish, tilapia. Neuroendocrinol. 64: 320–328.

Melamed, P., Rosenfeld, H., Elizur, A. and Yaron, Z. 1998. Endocrine regulation of gonadotropin and growth hormone gene transcription in fish. Comp. Biochem. Physiol. 119C: 325–338.

Mercure, F., Holloway, A.C., Tocher, D.R., Sheridan, M.A., Van der Kraak, G. and Leatherland, J.F. 2001. Influence of plasma lipid changes in response to 17β-oestradiol stimulation on plasma growth hormone, somatostatin, and thyroid hormone levels in immature rainbow trout. J. Fish Biol. 59: 605–615.

Moore, C.A., Kittilson, J.D., Ehrman, M.M. and Sheridan, M.A. 1999. Rainbow trout (*Oncorhynchus mykiss*) possess two somatostatin mRNAs that are differentially expressed. Am. J. Physiol. 46: R1553–R1561.

Mori, T. and Devlin, R.H. 1999. Transgene and host growth hormone gene expression in pituitary and nonpituitary tissues of normal and growth hormone transgenic salmon. Mol. Cell. Endocrinol. 149: 129–139.

Moriyama, S., Ayson, F.G. and Kawauchi, H. 2000. Growth regulation by insulin-like growth factor-I in fish. Biosci. Biotechnol. Biochem. 64: 1553–1562.

Oyama, H., Bradshaw, R.A., Bates, O.J. and Permutt, A. 1980. Amino acid sequence of catfish pancreatic somatostatin I. J. Biol. Chem. 255: 2251–2254.

Parmar, R.M., Chan, W.W., Dashkevicz, M., Hayes, E.C., Rohrer, S.P., Smith, R.G., Schaeffer, J.M. and Blake, A.D. 1999. Nonpeptidyl somatostatin agonists demonstrate that sst2 and sst5 inhibit stimulated growth hormone secretion from rat anterior pituitary cells. Biochem. Biophys. Res. Commun. 263: 276–280.

Patel, Y.C. 1999. Somatostatin and its receptor family. Front. Neuroendocrinol. 20: 157–198.

Patel, Y.C., Greenwood, M.T., Panetta, R., Demchyshyn, L., Niznik, H. and Srikant, C.B. 1995. The somatostatin receptor family. Life Sciences 57: 1249–1265.

Peake, G.T., Birge, C.A. and Daughaday, W.H. 1973. Alterations of radioimmunoassayable growth hormone and prolactin during hypothyroidism. Endocrinol. 92: 487–493.

Pesek, M.J., Howe, N. and Sheridan, M.A. 1998. Somatostatin binding to hepatocytes isolated from rainbow trout, *Oncorhynchus mykiss*, is modulated by insulin and glucagon. Gen. Comp. Endocrinol. 112: 183–190.

Pesek, M.J. and Sheridan, M.A. 1996. Fasting alters somatostatin binding to liver membranes of rainbow trout (*Oncorhynchus mykiss*). J. Endocrinol. 150: 179–186.

Planas, J.V., Mendez, E., Banos, N., Capilla, E., Castillo J., Navarro, I. and Gutierrez J. 2000. Fish insulin, IGF-I and IGF-II receptors: A phylogenetic approach. Am. Zool. 40: 223–233.

Plisetskaya, E.M. and Duan C. 1994. Insulin and insulin-like growth factor-I in coho salmon, *Oncorhynchus kisutch*, injected with streptozotocin. Am. J. Physiol. 267: R1408–R1412.

Plisetskaya, E.M. and Duguay, S.J. 1993. Pancreatic hormones and metabolism in ectotherm vertebrates: current views. In: The Endocrinology of Growth, Development, and Metabolism in Vertebrates. pp. 265–287. Edited by M.P. Schreibman, C. Scanes and P.K.T. Pang. Academic Press, New York.

Plisetskaya, E.M., Pollock, H.G., Rouse, J.B., Hamilton, J.W., Kimmel, J.R., Andrews, P.C. and Gorbman, A. 1986. Characterization of coho salmon (*Oncorhynchus kisutch*) islet somatostatins. Gen. Comp. Endocrinol. 63: 242–263.

Plisetskaya, E.M., Sheridan, M.A. and Mommsen, T.P. 1989. Metabolic changes in coho and chinook salmon resulting from acute insufficiency in pancreatic hormones. J. Exper. Zool. 249: 158–164.

Plisetsakaya, E.M., Swanson, P., Bernard, M. and Dickhoff, W.W. 1988. Insulin in coho salmon (*Oncorhynchus kisutch*) during smoltification. Aquaculture 72: 151–164.

Power, D.M., Llewellyn, L., Faustino, M., Nowell, M.A., Björnsson, B.Th., Einarsdottir, I.E., Canario, A.V.M. and Sweeney, G.E. 2001. Thyroid hormones in growth and development of fish. Comp. Biochem. Physiol. 130C: 447–459.

Rivier, J., Brazeau, P., Vale, W. and Guillemin R. 1975. Somatostatin analogs. Relative importance of the disulfide bridge and of the Ala-Gly side chain for biological activity. J. Med. Chem. 18: 123–126.

Rousseau, K., Le Belle, N., Marchelidon, J. and Dufour S. 1999. Evidence that corticotropin-releasing hormone acts as a growth hormone-releasing factor in a primitive teleost, the European eel (*Anguilla anguilla*). J. Neuroendocrinol. 11: 385–392.

Rousseau, K., Le Belle, N., Pichavant, K., Marchelidon, J., Chow, B.K.C., Boeuf, G. and Dufour S. 2001. Pituitary growth hormone secretion in the turbot, a phylogenetically recent teleost, is regulated by a species-specific pattern of neuropeptides. Neuroendocrinol. 74: 375–385.

Sheridan, M.A. 1994. Regulation of lipid metabolism in poikilothermic vertebrates. Comp. Biochem. Physiol. 107B: 495–483.

Sheridan, M.A., Eilertson, C.D. and Kerstetter, T.H. 1998. Changes in plasma somatostatin associated with seawater adaptation and stunting of coho salmon, *Oncorhynchus kisutch.* Aquaculture 168: 195–203.

Sheridan, M.A., Kittilson, J.D. and Slagter, B.J. 2000. Structure-function relationships of the signaling system for the somatostatin peptide hormone family. Am Zool. 40: 269–286.

Sheridan, M.A. and Mommsen, T.P. 1991. Effects of nutritional state on *in vivo* lipid and carbohydrate metabolism of coho salmon, *Oncorhynchus kisutch.* Gen. Comp. Endocrinol. 81: 473–483.

Slagter, B.J. and Sheridan, M.A. 2004. Differential expression of two somatostatin receptor subtype I mRNAs in rainbow trout (*Oncorhynchus mykiss*). J. Mol. Endocrinol. 32: 165–177.

Slagter, B.J. and Sheridan, M.A. 2002. Differential expression of somatostatin receptors. 84^{th} Annual Meeting of the Endocrine Society; Program and Abstracts. San Francisco, CA. P1-476.

Sohm, F., Manfroid, I., Pezet, A., Rentier-Delrue, F., Rand-Weaver, M., Kelly, P.A., Boeuf, G., Postel-Vinay, M., de Luze, A. and Edery, M. 1998. Identification and modulation of growth hormone-binding protein in rainbow trout (*Oncorhynchus mykiss*) plasma during seawater adaptation. Gen. Comp. Endocrinol. 111: 216–224.

Sullivan, C.V., Darling, D.S. and Dickhoff, W.W. 1987. Effects of triiodothyronine and propylthiouracil on thyroid function and smoltification of coho salmon (*Oncorhynchus kisutch*). Fish Physiol. Biochem. 4: 121–135.

Sweeting, R.M. and McKeown, B.A. 1986. Somatostatin reduces plasma growth hormone levels during seawater adaptation in coho salmon. Can. J. Zool. 64: 2062–2063.

Tannenbaum, G.S. and Epelbaum, J. 1999. Somatostatin. In: Handbook of Physiology, Section 7: The Endocrine System, V. Hormonal Control of Growth. pp. 221–265. Edited by J.L, Kostyo and H.M. Goodman. Oxford University Press, New York.

Trabucchi, M., Tostivint, H., Lihrmann, I., Blähser, S., Vallarino, M. and Vaudry, H. 2003. Characterization of the cDNA encoding a somatostatin variant in the chicken brain: comparison of the

distribution of the two somatostatin precursor mRNAs. J. Comp. Neurology. 461: 441–451.

Very, N.M., Knutson, D., Kittilson, J.D. and Sheridan M.A. 2001. Somatostatin inhibits growth of rainbow trout. J. Fish Biol. 59: 157–165.

Wong, A.O.L., Ng, S., Lee, E.K.Y., Leung, R.C.Y., Ho, W.K.K. 1998. Somatostatin inhibits (D-Arg^6, Pro^9-NEt) salmon gonadotropin-releasing hormone- and dopamine D_1-stimulated growth hormone release from perifused pituitary cells of Chinese Grass Carp, *Ctenopharyngodon idellus.* Gen. Comp. Endocrinol. 110: 29–45.

Yada T. and Hirano T. 1992. Inhibition of growth hormone synthesis by somatostatin in cultured pituitary of rainbow trout. J. Comp. Physiol B. 162: 575–580.

Yunker, W.K., Smith, S., Graves, C., Davis, P.J., Unniappan, S., Rivier, J.E., Peter, R.E. and Chang, J.P. 2003. Endogenous hypothalamic somatostatins differentially regulate growth hormone secretion from goldfish pituitary somatotropes *in vitro.* Endocrinol. 144: 4031–4041.

Zhang, Y. and Marchant. T.A. 1999. Identification of serum GH-binding proteins in the goldfish (*Carassius auratus*) and comparison with mammalian GH-binding proteins. J. Endocrinol. 161: 255–262.