Zoological Studies **36**(2): 79-89 (1997)

Zoological Studies

Review Article

Neuroendocrine Regulation of Growth Hormone Secretion and Growth in Fish

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ABSTRACT

Chun Peng and Richard E. Peter (1997) Neuroendocrine regulation of growth hormone secretion and growth in fish. *Zoological Studies* **36**(2): 79-89. Growth in fish is regulated in large part by the brain neuroendocrine - growth hormone (GH) - insulin-like growth factor axis. GH secretion is in turn regulated by multiple factors from the brain, with both stimulatory and inhibitory neurohormones acting on the somatotrophs seasonally.

Somatostatin is the primary inhibitor of basal and stimulated GH secretion. Norepinephrine and serotonin also have inhibitory actions on GH release. On the other hand, GH secretion is stimulated by a number of neuroendocrine factors, including growth hormone-releasing factor (GRF), dopamine (DA), gonadotropin-releasing hormone (GnRH), neuropeptide Y (NPY), thyrotropin-releasing hormone (TRH), cholecystokinin (CCK), bombesin (BBS), and activin. While GRF and DA are more potent in stimulating GH secretion in sexually regressed fish, GnRH, NPY, and TRH have greater stimulatory effects on GH secretion in sexually mature (i.e., prespawning) fish. Sex steroids, in particular estradiol, influence the responsiveness of the somatotrophs to neuroendocrine factors. The integrated action of sex steroids and neuroendocrine factors provides a basis for the seasonal regulation of growth hormone secretion.

The brain peptide systems regulating food intake are linked to the brain neuroendocrine regulation of GH secretion. Following a meal, goldfish characteristically show a short-term increase in serum GH concentrations, and then a decrease in serum GH concentrations to below premeal levels. BBS and CCK are involved in satiation and the changes in GH secretion following a meal in goldfish. Both the neuroendocrine regulation of GH secretion and the brain regulation of feeding are multifactorial. Understanding the integration of these systems presents a major challenge.

Key words: Fish, Growth hormone, Food intake, Neuropeptide, Monoamine.

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INTRODUCTION

Growth in fish is regulated by the brain neuroendocrine - growth hormone (GH) - insulin-like growth factor (IGF) axis. It is now well established that the control of GH secretion is multifactorial, with a balance of stimulatory and inhibitory neurohormones acting on pituitary somatotrophs on a seasonal basis. Somatostatin (SRIF) is the major inhibitor while a number of neuropeptides and amides stimulate GH secretion. Growth of fish can be stimulated by manipulation of selected neuroendocrine regulators of GH. It is obvious that growth cannot occur without adequate food intake; a linkage between food intake and GH secretion has recently been demonstrated in goldfish. In this article, we review how the secretion of GH, as well as food intake and growth, are regulated by brain neurohormones and neurotransmitters. The majority of the data reviewed are from studies of goldfish; however, comparisons are made with other fish species for which such data are available. The endocrinology of growth has recently been reviewed by Peter and Marchant (1995) and will not be repeated here.

NEUROENDOCRINE REGULATION OF GROWTH HORMONE SECRETION

Growth hormone-release inhibitory factors

1) Somatostatin

Somatostatin (SRIF) has been isolated and characterized in several fishes (Dixon and Andrews 1985, Plisetskaya et al. 1986, Conlon et al. 1988a, b, Conlon 1990). SRIF-14, derived from prepro-somatostatin-I in fishes, is identical to mammalian SRIF-14 (reviewed in Conlon 1990). Sequence analyses of cDNAs from fish species have indicated encoding for several variants of the SRIF amino acid structure, in addition to encoding for SRIF-14 (Shields et al. 1985, Conlon 1990, Moore et al. 1995). In fishes SRIF variants derived from preprosomatostatin-II include a 22-amino acid form in catfish (Andrews et al. 1984), 25-amino acid forms in salmon (Plisetskaya et al. 1986) and European eel (Conlon et al. 1988b), and 28-amino acid forms in anglerfish (Oyama et al. 1980), flounder, sculpin (Conlon 1990), and rainbow trout (Conlon 1990, Moore et al. 1995).

Immunoreactivity of SRIF-14 has been detected in the brain of several teleosts (reviewed in Peter 1986), and its inhibitory effect on GH secretion has been widely demonstrated in a number of species, including goldfish (reviewed in Peter and Marchant 1995), common carp (Lin et al. 1993a), tilapia (Melamed et al. 1995 1996), salmon (Le Bail et al. 1991), and trout (Luo et al. 1990, Luo and McKeown 1991). As in mammals, SRIF-14 is a potent inhibitor of basal as well as stimulated GH secretion in teleost fishes. However, SRIF-14 does not suppress expression of GH mRNA in rainbow trout (Yada and Hirano 1992) or tilapia (Melamed et al. 1996). Catfish SRIF-22 and salmon SRIF-25 are not effective in suppressing GH release in goldfish (Marchant et al. 1987, Marchant and Peter 1989).

In goldfish, SRIF-14 concentrations in various brain areas vary inversely with seasonal changes in serum GH levels and reproductive cycles (Marchant et al. 1989b). Specifically, forebrain concentrations of SRIF-14 are highest in autumn in sexually regressed goldfish and are lowest in sexually mature (i.e., prespawning) goldfish in spring; whereas, serum GH levels are highest in sexually mature goldfish in spring and early post-spawning goldfish in late spring or early summer, while lowest serum GH levels are in sexually regressed goldfish in autumn (Marchant and Peter 1986, Marchant et al. 1989b). This suggests that seasonal variations in GH reflect changes in the intensity of the SRIF-14 inhibitory tone.

2) Norepinephrine

Norepinephrine (NE) has been shown to inhibit GH secretion both in vivo and in vitro in goldfish. Chang et al. (1985) demonstrated that intraperitoneal injection of NE suppresses serum GH levels. More recently, Wong (1993) found that treatment of dispersed goldfish pituitary cells in primary culture with NE significantly decreased GH release, indicating that NE can act directly on somatotrophs to inhibit GH secretion. Similar to SRIF, NE can completely suppress the stimulatory actions of gonadotropin-releasing hormone (GnRH) and dopamine (DA) on GH release in vitro (Wong 1993). However, since NE is not detectable in goldfish pituitary (Sloley et al. 1991), the physiological role of NE in the regulation of GH secretion still remains to be determined.

3) Serotonin

Serotonin (5-HT) has inhibitory actions on GH secretion in the goldfish (Peter et al. 1990, Somoza and Peter 1991, Wong 1993). Intraperitoneal injection of 5-HT decreases serum GH levels in a dose-dependent fashion (Somoza and Peter 1991). In

addition, 5-HT suppresses GH release from dispersed goldfish pituitary cells in primary culture, indicating that it acts directly on somatotrophs (Wong 1993). Given that the concentrations of 5-HT in goldfish pituitary are very low (Sloley et al. 1991), additional studies are necessary to determine the physiological importance of 5-HT in the regulation of GH release in goldfish.

4) Glutamate

Both systemic injection and brain intraventricular injection of glutamate suppress serum GH levels in the goldfish (Trudeau et al. 1996). Glutamate-immunoreactive fibers are present throughout the pituitary in goldfish, with the highest concentration in the proximal pars distalis in proximity to the somatotrophs (Trudeau et al. 1996). These data suggest that glutamate normally functions to inhibit GH secretion in goldfish.

Growth hormone-release stimulatory factors

1) Growth hormone-releasing factor

In mammals it is generally accepted that GH-releasing factor (GRF) is a primary stimulator of GH secretion (for review see Harvey 1993). Peter et al. (1984) demonstrated that intraperitoneal injection of human GRF1-40 fragment caused an increase in serum GH levels in goldfish. GRF-like immunoreactivity has been shown in the brain and pituitary of teleosts, such as codfish (Pan et al. 1985), sea bass (Moons et al. 1989), rainbow trout (Luo and McKeown 1989a), eel, carp, goldfish, and salmonids (Olivereau et al. 1990, Parker and Sherwood 1990). GRF has been isolated and characterized from common carp hypothalamus (Vaughan et al. 1992). Complementary DNA encoding a GRF-like peptide has been cloned from salmon (Parker et al. 1993), catfish (McRory et al. 1995), and zebrafish (Delgado et al. 1996). Fish GRFs only share 35%-40% identities with human GRF. Also, while zebrafish, carp, and salmon GRFs are very similar, catfish GRF has only 58% identity to salmon and zebrafish GRFs and 60% identity to carp GRF, respectively. Interestingly, fish GRFs are encoded by the same gene as the pituitary adenylate-cyclase activating polypeptide, while in mammals these 2 peptides are encoded by separate genes (Parker et al. 1993, McRory et al. 1995).

Synthetic common carp GRF (cGRF) stimulates GH release from perifused goldfish pituitary cells and induces an increase in serum GH levels in goldfish following intraperitoneal injection (Vaughan et al. 1992). The effects of GRF on GH release from perifused goldfish pituitary cells are additive to 2 other GH simulators, DA and GnRH (Peng 1993), but are completely abolished by SRIF-14 (Vaughan et al. 1992). Pituitary cells taken from sexually regressed goldfish are much more responsive to cGRF than those from sexually recrudescent fish (C Peng and RE Peter unpubl. results), suggesting that gonadal steroids may decrease the responsiveness of somatotrophs to GRF. The stimulatory effect of cGRF on GH release has also been observed in rainbow trout (Luo and McKeown 1989b 1991, Luo et al. 1990) and tilapia (Melamed et al. 1995); stimulation of GH release by human GRF was confirmed in rainbow trout (Blaise et al. 1995). However, cGRF is effective in stimulating GH release from perifused tilapia pituitary fragments only at a dose level of 1 μM (Melamed et al. 1995). In the same study, it was demonstrated that human GRF stimulates GH secretion both in vivo and in vitro (Melamed et al. 1995).

2) Dopamine

Following brain intraventricular injection of dopamine (DA), or intraperitoneal injection of the DA D1/D2 receptor agonist apomorphine, or the DA precursor L-DOPA, serum GH levels in goldfish increase (Chang et al. 1985). The actions of DA on GH secretion are directly at the pituitary level as apomorphine stimulates GH release from dispersed goldfish pituitary cells in static and perifusion culture (Chang et al. 1990b). Using a combination of dopamine receptor agonist and antagonist drugs, Chang et al. (1990b) and Wong et al. (1992) found that the stimulatory actions of DA on GH release are mediated by the D1 receptor. D1 receptors have been characterized in goldfish pituitary cells using enzymatically dispersed mixed cell populations as well as enriched somatotrophs (Wong et al. 1993a). This is the first demonstration of D1 receptors in a vertebrate pituitary. Autoradiographic studies reveal that the D1 specific binding sites are localized in the proximal pars distalis of the goldfish pituitary where the somatotrophs are located (Wong et al. 1993a), further supporting the involvement of D1 receptors in the DA regulation of GH secretion.

The stimulatory action of DA on GH release varies with the seasonal reproductive cycle, being highest in sexually regressed fish, intermediate in recrudescent fish, and lowest in sexually mature fish (Wong et al. 1993b,c). In addition, the in vivo and in vitro actions of DA and their analogs on GH secretion can be blocked by SRIF (Wong et al. 1993b,c). Similarly, DA and D1 agonists also

stimulate GH secretion in common carp (Lin et al. 1993a,b) and tilapia (Melamed et al. 1995 1996 1997).

Stimulation of GH release by DA activation of D1 receptors has been demonstrated to involve the cyclic AMP (cAMP) and protein kinase A (PKA) 2nd messenger system in goldfish (Chang et al. 1994 1996). The DA stimulation of GH release by the cAMP-PKA system in tilapia also stimulates GH gene transcription (Melamed et al. 1996 1997).

3) Gonadotropin-releasing hormone

In goldfish, presence of both salmon gonadotropin-releasing hormone (sGnRH) and chicken GnRH-II (cGnRH-II) has been demonstrated in the brain using chromatographic and immunological techniques (Yu et al. 1988). Although GnRH has been recognized primarily as a stimulator of gonadotropin (GTH) secretion, Marchant et al. (1989a) first demonstrated that mammalian GnRH (mGnRH) and sGnRH, as well as their superactive analogs, stimulated GH release both in vitro and in vivo in goldfish. Both sGnRH and cGnRH-II also stimulate GH release from dispersed goldfish pituitary cells (Chang et al. 1990a,b), suggesting that GnRH acts directly on somatotrophs. In addition to goldfish, GnRH has also been shown to stimulate GH secretion in common carp (Lin et al. 1993a) and tilapia (Melamed et al. 1995). SRIF-14 can block the stimulatory actions of GnRH peptides on GH secretion in all species studied so far. Notably, GnRH peptides did not stimulate GH release either in vivo or in vitro in rainbow trout (Blaise et al. 1995).

Specific binding of sGnRH to goldfish pituitary somatotrophs has been demonstrated (Cook et al. 1991). Peptide structure-activity studies suggest that GnRH receptors on somatotrophs are functionally distinct from GnRH receptors on gonadotrophs. GnRH agonists, [His^8]-, [Leu^8]-, [Met^8]- and [Tyr^8]-mGnRH, each were equipotent with sGnRH in releasing GH, but had significantly lower potency than sGnRH in releasing gonadotropin-II from goldfish pituitary in vitro (Habibi et al. 1992). Furthermore, a GnRH antagonist, [Ac-Δ^3-Pro^1, 4FD-Phe^2, D-$Trp^{3,6}$]-sGnRH, blocked the effect of sGnRH on GTH-II release but stimulated GH release by itself (Murthy et al. 1993, Murthy and Peter 1994). In contrast, 2 antagonists, [Ac-Δ^3-Pro^1, 4FD-Phe^2, D-Trp^3, D-Arg^6]-mGnRH (Murthy and Peter 1994) and [Ac-D(2)-Nal^1, 4Cl-D-Phe^2, D(3)-$Pal^{3,6}$, Arg^5, D-Ala^{10}]-mGnRH (Murthy et al. 1994a) suppressed GH release but increased GTH-II levels. It may be possible, therefore, to design GnRH analogues which specifically stimulate GH secretion without affecting GTH release.

Circulating GH levels in sexually mature goldfish decrease following intraperitoneal injection of the GnRH antagonist [Ac-Δ^3-Pro^1, 4FD-Phe^2, D-$Trp^{3,6}$]-mGnRH (Murthy et al. 1994b), indicating that GnRH is a physiological regulator of basal GH secretion. Injection of sGnRH in goldfish has a potent stimulatory action on the expression of GH mRNA in the pituitary (Mahmoud et al. 1996). Contrary to this, exposure of tilapia pituitary cells to GnRH increases GH release without increasing GH gene expression (Melamed et al. 1996 1997). GnRH peptides activate the protein kinase C 2nd messenger pathway leading to GH release in goldfish (Chang et al. 1994 1996, Wong et al. 1994) and tilapia (Melamed et al. 1996 1997). On this basis, it may be species dependent whether GnRHs, and other peptides that activate the protein kinase C 2nd messenger pathway leading to GH release, also activate GH gene expression.

Estradiol plays a role in the regulation of seasonal changes in circulating GH levels in goldfish; implantation of estradiol causes an increase in serum GH levels in female goldfish in a dose-dependent manner (Trudeau et al. 1992). Pituitaries from sexually regressed and gonadal recrudescing fish pretreated with estradiol have greater magnitudes of GH release in response to sGnRH in vitro (Trudeau et al. 1992). Treatment of goldfish in vivo with testosterone or treatment of goldfish pituitary fragments in vitro with testosterone causes a dose-dependent increase in the expression of GH mRNA (Huggard and Habibi 1995, Huggard et al. 1996). This indicates that at least part of the positive feedback actions of sex steroids on GH secretion are directly at the level of the pituitary.

4) Neuropeptide

Neuropeptide Y (NPY), a 36-amino acid peptide, was first isolated from porcine brain and later characterized in various vertebrates, including goldfish (Blomqvist et al. 1992). The presence of NPY in fish was first demonstrated in goldfish by immunological and chromatographic studies (Kah et al. 1989). Immunoreactive NPY nerve fibers can be found in goldfish pituitary, especially in close relationship with somatotrophs (Kah et al. 1989), suggesting a role for NPY in regulating GH release. Peng et al. (1990) demonstrated that NPY is highly potent in stimulating GH release from goldfish pituitary fragments; human NPY and goldfish NPY are equipotent in stimulating GH release in vitro (Peng et al. 1990 1993b). Serum GH concentrations in goldfish also increase following intra-

peritoneal injection of NPY (Peng et al. 1993b). Desensitization of GH responses to NPY occurs when goldfish pituitary fragments are challenged by repeated pulses of NPY (Peng et al. 1990 1993a). This down-regulation of GH response induced by NPY is dose- and time-dependent, and recovery occurs within about 90 min (Peng et al. 1990 1993a).

The stimulation of GH release by NPY has at least 2 components, a direct action on the pituitary cells and an indirect action through the release of GnRH from neurosecretory terminals in the pituitary (Peng et al. 1993a). NPY stimulates GH release from mixed populations of enzymatically dispersed goldfish pituitary cells, as well as enriched somatotrophs (Peng et al. 1993a), indicating that NPY exerts its stimulation on GH secretion by acting directly on the somatotrophs. On the other hand, NPY stimulates GnRH release from the neurosecretory nerve terminals remaining in goldfish pituitary fragments and the stimulatory effects of NPY on GH release from pituitary fragments can be partially blocked by a GnRH antagonist (Peng et al. 1993a). Therefore, the actions of NPY on GH release appear to be in part mediated by GnRH. The magnitude of the in vitro GH response to NPY changes with the seasonal reproductive cycles, with the greatest responses observed in sexually mature goldfish (Peng et al. 1993c); implantation of testosterone into sexually regressed goldfish significantly enhanced the in vitro GH response to NPY (Peng et al. 1993c). This may be due to actions of the sex steroid on the GnRH system, as implantation of testosterone in sexually regressed goldfish enhances the GnRH release response to NPY (Peng et al. 1993c). The stimulatory effects of NPY on perifused pituitary fragments (Peng et al. 1993b) or enriched somatotrophs (Peng et al. 1993a) can be blocked by SRIF-14, indicating the interactive nature of the stimulatory actions of NPY and the inhibitory actions of SRIF-14.

5) Thyrotropin-releasing hormone

Thyrotropin-releasing hormone (TRH) has been shown to stimulate GH secretion in a wide range of vertebrates including mammals, birds, reptiles, and amphibians, and is the primary regulator of GH release in birds (Harvey 1990). In goldfish, TRH increases serum GH levels following intraperitoneal injection (Cook and Peter 1984) and stimulates GH release from perifused pituitary fragments (Trudeau et al. 1992). Similar to GnRH and NPY which show greatest stimulatory actions on GH release in sexually mature goldfish, pituitaries from sexually mature fish have a greater sensitivity to TRH than pituitaries from sexually regressed fish (Trudeau et al. 1992). The GH response to TRH in sexually regressed fish can be increased by pretreatment with estradiol (Trudeau et al. 1992). Lin et al. (1993b) have also demonstrated that TRH stimulates GH release from perifused common carp pituitaries and that SRIF-14 blocks the stimulatory actions of TRH. However, a recent study of tilapia shows that while TRH stimulates GH secretion in vivo, it has no effect on GH release from isolated pituitary fragments (Melamed et al. 1995), suggesting that TRH does not act directly on the pituitary to regulate GH secretion in this species.

6) Cholecystokinin

Himick et al. (1993) have reported the presence of cholecystokinin (CCK)-like IR in goldfish pituitary, especially within fibers innervating the proximal pars distalis, the region of the pituitary containing somatotrophs and gonadotrophs. Using in vitro perifusion of goldfish pituitary fragments, it was found that the sulfated form of CCK-8 (CCK-8s) is highly effective in stimulating GH release (Himick et al. 1993). Unlike other GH-regulators which show seasonal variation of effectiveness, there is no significant difference in GH response to CCK between sexually regressed and recrudescent fish (Himick et al. 1993). However, there is a tendency for pituitary fragments from sexually regressed goldfish to have a greater GH responsiveness to CCK-8s than pituitary fragments from sexually recrudescing fish; the gonadotropin-II responsiveness of pituitary fragments from sexually regressed fish is significantly greater than that of sexually recrudescing fish (Himick et al. 1993). Notably, both systemic injection and brain intraventricular injection of CCK-8s cause a short-term increase in serum GH levels in goldfish (Himick and Peter 1994b; see below for further discussion).

Binding characteristics and distribution of brain and pituitary receptors for CCK have been characterized in goldfish (Himick et al. 1996). A single high affinity binding site for CCK and gastrin peptides was demonstrated. A high density of binding sites was found in the proximal pars distalis, where somatotrophs and gonadotrophs are located, confirming that CCK is directly involved in the regulation of GH secretion.

7) Bombesin

Bombesin (BBS) is a tetradecapeptide first isolated from skin extracts of the frog, *Bombina*

bombina (Anastasi et al. 1971). In goldfish, BBS-like IR is present in the brain and pituitary, suggesting a role for BBS in the neuroendocrine regulation of pituitary hormone secretion (Himick and Peter 1995a). Indeed, perifusion of goldfish pituitary fragments with pulses of BBS results in a dose-dependent stimulation of GH release (Himick and Peter 1995a). BBS also stimulates GH secretion in vivo; intraperitoneal injection or brain intraventricular injection of BBS significantly increases serum GH levels (Himick et al. 1993). The demonstration of BBS binding sites in goldfish pituitary (Himick et al. 1995) further supports the idea of involvement of BBS in the regulation of GH secretion. However, the relative importance of BBS in regulation of GH secretion is not clear because the distribution of BBS/gastrin-releasing peptide IR fibers in the pituitary is primarily in the neurointermediate lobe, or along the border of the neurointermediate lobe and the proximal pars distalis, with relatively few fibers directly in the proximal pars distalis (Himick and Peter 1995a). Likewise, autoradiographic localization of BBS/gastrin-releasing peptide binding sites demonstrates a high density in the neurointermediate lobe, and a relatively low density in the proximal pars distalis (Himick et al. 1995).

8) Activin

Immunocytochemical staining of goldfish pituitary indicates that the activin βA subunit is predominantly produced in the pituitary in somatotrophs, whereas staining for βB in somatotrophs is relatively weak and staining for the α-subunit of inhibin is localized to fibers in the neurointermediate lobe (Ge and Peter 1994). These results suggest that goldfish somatotrophs produce activin. Recent studies confirm the expression of mRNA encoding activin β subunits in the pituitary of goldfish (Ge et al. 1997). Porcine inhibin and activin both stimulate GH release (Ge and Peter 1994) and gonadotropin-II release (Ge et al. 1992) from perifused goldfish pituitary fragments, suggesting that activin produced by somatotrophs may have autocrine and paracrine actions, respectively, in the pituitary.

NEUROENDOCRINE REGULATION OF FOOD INTAKE AND GROWTH

Regulation of food intake

Mainly through brain electrical stimulation and lesioning studies, it has been established that food intake is regulated by the hypothalamic ventromedial-posterior and lateral lobes in fish (for review see McLean and Donaldson 1993). A number of neuropeptides have been shown to regulate feeding in fish. BBS suppresses food intake within minutes following intraperitoneal injection or brain intraventricular injection (Himick and Peter 1994a). Similar treatments with CCK-8s also acutely suppress food intake in goldfish (Himick and Peter 1994b). Immunocytochemical studies demonstrate that BBS and CCK are present in the brain hypothalamic feeding area of goldfish (Himick et al. 1993, Himick and Peter 1995a) and other teleosts (Notemboom et al. 1981, Batten et al. 1990, Moons et al. 1992). Receptor radioautography studies indicate the presence of BBS (Himick et al. 1995) and CCK (Himick et al. 1996) receptors in the brain hypothalamic feeding area of goldfish. Specific CCK binding sites have also been detected in the hypothalamic feeding area of the sea bass (Moons et al. 1992). Together these data provide strong evidence that BBS and CCK are involved in satiation in goldfish and other fish. In addition, corticotropin-releasing factor has also been reported to suppress food intake in goldfish following either intraperitoneal injection or brain intraventricular injection (De Pedro et al. 1993).

Neuropeptide Y, which plays a prominent role in stimulating food intake in mammals, is present in the goldfish ventromedial-posterior hypothalamus and hypothalamic inferior lobes (Pontet et al. 1989). Our recent studies have shown that NPY receptors are localized in the feeding regulatory center (BA Himick, SR Vigna and RE Peter unpubl. results). Neuropeptide Y gene expression in the preoptic region of fasting chinook salmon increases (Silverstein et al. 1996), providing additional evidence for involvement of NPY in the regulation of food intake. Direct studies have not been done, to our knowledge, on neuropeptides that stimulate food intake in fish.

GH has also been shown to play an important role in regulating food intake. Chronic administration of GH results in an increase in food intake and subsequent improved food conversion efficiency in several teleosts (for review see Peter 1995). Injection of GH into rainbow trout also increases the appetite (Johnson and Bjornsson 1994). In goldfish, we have also found a relationship between circulating serum GH levels and feeding. When fed with a 2% wet body weight (bw) ration, fish exhibit an acute elevation in serum GH 30 min after feeding (Himick and Peter 1995b). This

initial rise in serum GH levels, which occurs independently of body weight, is followed by a sharp decrease and then, over the next 3 h, a more gradual decrease to serum GH levels significantly lower than in unfed control fish (Himick and Peter 1995b). Since treatment with CCK-8s and BBS concomitantly suppresses feeding and increases serum GH levels (Himick et al. 1993, Himick and Peter 1994a,b), it is conceivable that these peptides are involved in satiation and the changes in GH secretion following a meal in fish.

Regulation of growth rate

It has been demonstrated that administration of neurohormones or their analogs that stimulate GH secretion increases growth rates in fishes. Marchant et al. (1989a) demonstrated that a series of intraperitoneal injections of a GnRH superactive analog stimulates linear growth rates in goldfish. C Peng and RE Peter (unpubl. results) have also shown that intramuscular injection of goldfish with a slow-release preparation of [D-Trp^6]-mGnRH increases serum GH levels and stimulates linear and somatic growth rates. Oral administration of apomorphine, a dopamine agonist, has also been shown to significantly increase both body length and weight growth rates in goldfish (Wong et al. 1993c). Blockade of SRIF inhibitory tone on GH secretion by a series of intraperitoneal injections of SRIF antibody in juvenile chinook salmon also results in a significant increase in growth rates (Mayer et al. 1994). Using a food carrier vehicle developed by Syndel Laboratories, we have recently found that the feeding of a combination of 2 long-lasting analogs of selected neuroendocrine factors results in a highly significant increase in GH secretion and growth rates of goldfish (RE Peter, JP Chang, C Neumann, and S Humphries unpubl. results). These results indicate that administration of selected neuroendocrine factors may be a highly effective means of stimulating growth rates of farmed fish.

SUMMARY

Our current understanding of the neuroendocrine control of GH secretion, feeding, and growth in fish is summarized in Figure 1. This regulation is multifactorial in nature. SRIF-14 is the primary inhibitory control of basal and stimulated GH release. NE and 5-HT also inhibit GH secretion. On the other hand, GRF, DA, GnRH, NPY, TRH, CCK, BBS, and activin all stimulate GH secretion in goldfish. Studies on factors stimulating GH release in other teleosts are limited, generally showing agreement with findings in goldfish. There are some notable differences, however; in particular, GH release in rainbow trout does not respond to GnRH.

It is not clear whether there is a primary stimulator of GH release in goldfish. Our data suggest that a group of factors may be dominant at 1 sexual stage and another group at another sexual stage. In this regard, gonadal steroids play an important role in altering the responsiveness of GH to these regulators. Based on the seasonality of GH secretion in goldfish, the GH-release stimulatory factors can be divided into 3 groups: GRF and DA are more effective in sexually regressed fish; GnRH, NPY, and TRH are more potent in sexually mature fish; and, the effect of CCK has no clear seasonality. It is not known whether there are seasonal variations in GH responsiveness to BBS and activin.

Long-term treatment with neuroendocrine factors that stimulate GH secretion also increases growth rates in goldfish. Food intake is stimulated by GH but inhibited by CCK and BBS in goldfish. Evidence indicates that BBS and CCK are involved in satiation and changes in growth hormone secretion following a meal in goldfish. Understanding the integration of neuroendocrine regulation of GH secretion and food intake presents a major challenge.

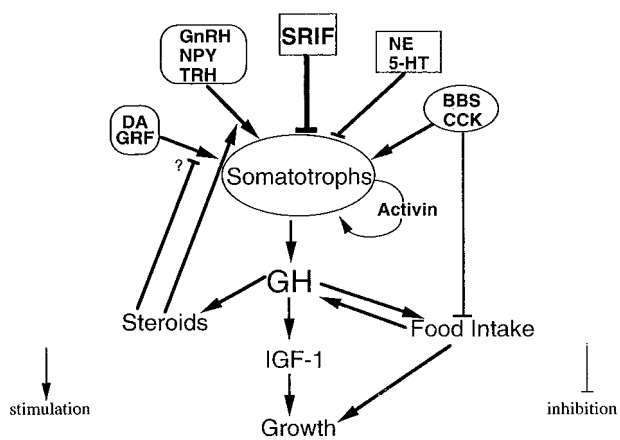

Fig. 1. Model of the multifactorial neuroendocrine regulation of growth hormone (GH) secretion, food intake, and growth in goldfish. Abbreviations: bombesin, BBS; cholecystokinin, CCK; dopamine, DA; GH-releasing factor, GRF; gonadotropin-releasing hormone, GnRH; neuropeptide Y, NPY; norepinephrine, NE; serotonin, 5-HT; somatostatin, SRIF; thyrotropin-releasing hormone, TRH.

Acknowledgements: This research is supported in part by Natural Sciences and Engineering Research Council of Canada grants to CP and REP. CP is a recipient of a Women's Faculty Award from the Natural Sciences and Engineering Research Council of Canada.

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魚類生長激素分泌及生長之神經內分泌調節

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魚類的生長是由腦神經內分泌系統一生長激素 (GH) 一類胰島素生長因子 (IGF) 所控制的。腦中多種刺激因子和抑制因子能作用於腦下垂體生長激素分泌細胞，而調節生長激素的分泌，而且這些因子對生長激素分泌的調節作用能隨生殖季節而變化。

促生長激素釋放抑制因子 (SRIF) 是最主要的抑制因子。它不但能抑制生長激素的基礎分泌，而且還能阻斷所有釋放因子對生長激素分泌的促進作用。去甲腎上腺素 (NE) 和5羥色胺 (5-HT) 對生長激素的分泌也起抑制作用。有幾種神經內分泌因子，包括生長激素釋放因子 (GRF)，多巴胺 (DA)，促性腺激素釋放因子 (GnRH)，神經肽Y (NPY)，促甲狀腺素釋放因子 (TRH)，胰酶分泌素 (CCK)，bombesin (BBS) 和activin，都已證明能夠促進生長激素分泌。GRF和DA在性腺退化期促進生長激素分泌的作用最強，而GnRH，NPY和TRH的作用則於性腺成熟期最爲明顯。性腺類固醇，尤其是雌二醇，能調節生長激素分泌細胞對這些神經內分泌因子的反應。正是這種性激素和神經內分泌因子之間的相互作用導致了魚類生長激素分泌的季節性調控。

腦中調節食物攝入量和生長激素分泌的系統是相關連的。在金魚中，血液生長激素的含量通常在進食後有一個短暫的上升，接著下降到低於進食前水準。BBC和CCK能同時控制食慾和進食後生長激素的分泌。實驗證明在魚類中，生長激素的分泌和食物攝取都受到多重神經內分泌因子的調節，目前面臨的難題是如何去瞭解這兩種控制系統之間的相互關係。

關鍵詞：魚類，生長激素，進食，神經肽，單胺。

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