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The Neuroendocrine Secretion Regulates Growth Hormone Release in Teleost Fish

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The growth hormone (GH) secretion in cyprinids and other teleost species is apparently regulated by several neuroendocrine factors working together. Somatostatin is the primary inhibitor of basal and stimulated GH release while the other inhibitors are norepinephrine and serotonin. The GH secretion is stimulated by GH- releasing hormone, gonadotropin-releasing hormone, thyrotropin-releasing hormone, cholecystokinin, bombesin, neuropeptide Y, dopamine and galanin. The growth rate of cultured fish may be stimulated by neuroendocrine factors added to food, or by administration of GH or recombinant GH preparations. Techniques for enhancing growth rates of cultured fish are in an experimental stage.

Key words: Growth hormone, growth-hormone releasing factor, somatostatin, bombesin, dopamine, galanin, aquaculture.

Growth hormone release from the pituitary gland is generally not autonomous. Its release appears to be regulated by secretion of neuroendocrine system. The neuroendocrine regulation of GH secretion in teleosts and other piscine groups is multifactorial with a balance of stimulatory or inhibitory inputs to somatotrophs. The control of GH release is primarily mediated through the hypothalamus in vertebrates. This has come out from the studies in mammalian and, to a lesser extent in avian species (Ball, 1981; Hall *et al.*, 1986). The neuroendocrine regulation of GH secretion in teleost fish and other vertebrates has been reviewed recently (Harvey, 1993; 1995; Peter & Marchant, 1995). Hormone manipulation is currently used in aquaculture for enhancing the growth rate in various teleost species of economic importance. The objective of this review is to summarize the information available on the main neuroendocrine secretions regulating the growth hormone (GH) release.

The hypothalamic peptides and or amines that regulate GH-releasing and GH-inhibiting activity are discussed in the present review so as to focus attention on the peptides and amines that are involved in GH regulation in teleosts.

Growth-Hormone-Releasing Factor

Intraperitoneal injection of human growth-hormone-releasing factor 1-40 (GRF_{1-40}) fragment stimulates an increase in serum GH levels in goldfish, suggesting that the GRF system is present in teleost fish (Peter *et al.*, 1984). GRF, a 45-amino acid peptide was found to be present in brain extracts of coho and chum salmon (Parker & Sherwood, 1990) and in hypothalamic extract of common carp (Vaughan *et al.*, 1992). The synthetic replicate of the GRF peptide is highly potent (50% effective dose - ED

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50, ~0.08 nM) in stimulating GH release from pituitary glands of cultured goldfish and in elevating serum GH levels 30 min after intraperitoneal injection (Vaughan *et al.*, 1992). Synthetic carp GRF (cGRF) is also effective in stimulating GH release from rainbow trout pituitaries *in vitro* (Luo & Mckeown, 1991; Luo *et al.*, 1990).

Somatostatin

Somatostatin-14 (SRIF-14) is present in several teleost fish. However three variants of somatostatin, SRIF-28, a unique SRIF-22 and SRIF-25 have also been found in anglerfish, catfish and salmon respectively (Reichlin, 1983; Peter, 1986; Plisetskaya *et al.*, 1986). SRIF-14 is a potent inhibitor of GH level both *in vivo* (Cook & Peter, 1984) and *in vitro* (Marchant *et al.*, 1987) in goldfish. Marchant & Peter (1989) observed that SRIF-14 inhibit GH secretion from perifused fragments of the goldfish, but at the same concentrations, SRIF-25 is completely ineffective in altering GH release. There is a seasonal variation in concentrations of serum GH level in goldfish, with the highest levels in the spring, in fish that are in pre-spawning period and the lowest levels, in sexually regressed fish in the autumn (Marchant & Peter, 1986; Marchant *et al.*, 1989). The concentrations of SRIF-14 in various brain regions of the goldfish also vary on a seasonal basis inverse to the seasonal variation in concentrations of serum GH (Marchant *et al.*, 1989), suggesting that the seasonal variations in GH reflect changes in the intensity of the SRIF-14 inhibitory tone (Peter & Marchant, 1995).

Thyrotropin-releasing-hormone

Thyrotropin-releasing hormone (TRH) not only stimulates pituitary TSH secretion but also releases GH in all vertebrate groups (Harvey 1990, 1993). Intraperitoneal injection of TRH in goldfish stimulates an increase in serum GH levels (Cook & Peter, 1984). According to Trudeau *et al.* (1992) TRH is highly potent in stimulating GH release from perifused pituitary fragment of goldfish and the pituitaries from sexually mature fish have a greater sensitivity to TRH than pituitaries from sexually regressed fish. Lin *et al.* (1993) have demonstrated that the common carp pituitary is also highly responsive to TRH *in vitro.* They also reported that SRIF-14 blocks the stimulatory actions of TRH on GH release in the common carp.

Gonadotropin-releasing hormone

Gonadotropin-releasing hormone (GnRH) is a decapeptide having eight distinct forms in the vertebrates (Sherwood *et al.*, 1994). Recently a ninth form of GnRH has been identified and referred to as seabream GnRH (sbGnRH) (Powell *et al.*, 1995). Marchant *et al.* (1989) was the first to demonstrate that mammalian GnRH (mGnRH) and salmon GnRH (sGnRH) and superactive analogues of mGnRH and sGnRH were effective in stimulating GH release *in vivo* and *in vitro* in gold fish. sGnRH and chicken GnRH-II (cGnRH-II) stimulate GH release from the dispersed goldfish pituitary cells in static or perifusion culture (Chang *et al.*, 1990 a,b). sGnRH and recently discovered cat fish GnRH (cfGnRH) (Ngamvongchon *et al.*, 1992) and dog fish GnRH (dfGnRH) (Lovejoy *et al.*, 1992) are similar in potency to stimulate GH release from the perifused goldfish pituitary fragments (Peter & Marchant, 1995). In structure-activity studies on putative GnRH antagonists in the goldfish, analogues with D-Arg6 were generally stimulatory to GH release in the goldfish pituitary *in vitro*, contrary to their usual antagonistic activity in mammals (Murthy *et al.*, 1994a,b). Marchant *et al.* (1989) demonstrated that multiple intraperitoneal injection of a GnRH superactive agonist analogue stimulated linear growth rates in goldfish. On this basis it is clear that GnRH peptides play an important role in the regulation of GH secretion in goldfish and common carp, especially in fish undergoing gonadal development and in sexually mature fish (Peter & Marchant, 1995).

Cholecystokinin

Cholecystokinin (CCK) is an 8-amino acid peptide and its sulfated form is highly effective in stimulating GH release from the perifused goldfish pituitary fragments (Himick *et al.*, 1993). This novel action of CCK-8s on GH release is supported by the observation of CCK/gastrin-like immunoreactive nerve fiber in the proximity of somatotrophs in the proximal pars distalis of the goldfish (Himick *et al.*, 1993).

Bombesin

Bombesin (BBS), a tetradecapeptide, is widely distributed throughout the central nervous system and is released by hypothalamic nerve endings (Harvey, 1995) BBS-like immunoreactivity has recently been observed by Himick & Peter (1995) in the forebrain and pituitary of goldfish. BBS injection alters circulating serum GH levels in goldfish (Himick & Peter, 1994) and perifusion of gold fish pituitary fragments with BBS results in the release of GH (Himick & Peter, 1995). The direct stimulation of GH secretion following perifusion of goldfish pituitary fragments with BBS further suggests that it is capable of functioning as a neuroendocrine modulator in the fish (Himick & Peter, 1995).

Neuropeptide Y

The hypophysiotropic role of neuropeptide Y (NPY) is indicated by its wide distribution in the central nervous system and concentration in hypothalamus (Harvey, 1995). NPY is a 36-aminoacid peptide and was first demonstrated in goldfish by immunological and chromatographic studies (Kah *et al.*, 1989). Peng *et al.* (1990) documented that NPY is highly potent in stimulating GH release from perifused goldfish pituitary fragments. Human NPY and goldfish NPY(goldfish NPY has 5-amino acid substitutions relative to human NPY; Blomqvist *et al.*, 1992) are equipotent in stimulating GH release *in vitro* in goldfish (Peng *et al.*, 1993b). The stimulation of GH release by NPY involves Y1 and Y2 - type receptors suggesting that the GH response induced by NPY maybe primarily dependent on stimulation of GnRH release and subsequent actions of GnRH on the somatotrophs (Peng *et al.*, 1993a). NPY stimulates the greatest magnitude of GH release in pituitaries from sexually mature goldfish (Peng *et al.*, 1990; 1993c). The presence of immunoreactive NPY nerve fibers in close association with somatotrophs in the proximal pars distalis in goldfish (Kah *et al.*, 1989) provides strong support for a role of NPY in regulating GH release.

Dopamine

Dopamine (DA) - containing neurons are found in significant amounts in the hypothalamus and some of these neurons project to the median eminence in which DA and GRF appear to be colocalized in nerve fibers (Harvey, 1995). The dopamine agonist, apomorphine stimulates GH release from dispersed goldfish pituitary cells in statics and perifusion culture (Chang *et al.*, 1990b). This provides a direct evidence for DA stimulation of GH release, a unique discovery for the vertebrate pituitary. The stimulatory actions of DA on GH release is most prominent in sexually regressed goldfish (Wong *et al.*, 1993a,b). The *in vitro* actions of DA and apomorphine and the *in vivo* actions of apomorphine in stimulating GH release in goldfish (Wong *et al.*, 1993a,b) and the *in vitro* stimulatory effects of apomorphine on GH release in common carp (Lin *et al.*, 1993) can be blocked by SRIF-14. Treatment of goldfish by intraperitoneal injection with apomorphine (Wong *et al.*, 1993a) or by addition of apomorphine to the food (Wong *et al.*, 1993b) increases serum GH levels and growth rates. Thus DA plays an important role in the regulation of GH secretion in goldfish, carp and other cyprinids, particularly those in a sexually regressed condition (Peter & Marchant, 1995).

Serotonin and Norepinephrine

Both serotonin (5-HT) and norepinephrine (NE) have inhibitory actions on GH levels *in vitro* in goldfish (Peter *et al.*, 1990; Somoza & Peter, 1991; Wong, 1993). The intraperitoneal injection of NE also suppresses GH level in the goldfish (Chang *et al.*, 1985). The actions of 5-HT on suppression of GH release are dose dependent (Somoza & Peter, 1991). Wong (1993) described that both NE and 5-HT suppress GH release from dispersed goldfish pituitary cell in primary culture, indicating that the actions are direct on somatotrophs. However, additional studies are necessary to demonstrate the physiological importance of 5-HT and NE in regulating GH release in teleost fish, as the concentration of 5-HT is very low and that the NE is not detectable in goldfish pituitary (Peter & Marchant, 1995; Sloley *et al.*, 1991).

Galanin

Galanin (GAL), a 29-amino acid peptide was originally isolated and sequenced from porcine small intestine (Tatemoto *et al.*, 1983) and also from stomach extract of rainbow trout, *Onchorhynchus mykiss* (Anglade *et al.*, 1994). GAL-like immunoreactivity is richly present in cell bodies in the arcuate, paraventricular and supraoptic nuclei of the hypothalamus, from which immunoreactive fibers that contain GRF terminate in the median eminence (Harvey, 1995). Recently, Prasad Rao *et al.* (1996) have shown the sexual dimorphism of GAL-like immunoreactivity in the brain and pituitary of goldfish. Localization of GAL-like immunoreactive perikarya in cell bodies of hypothalamic nuclei and in nerve terminalis of median eminence suggested a possible neuroendocrine role for anterior pituitary function. There are evidences that GAL enhances GH and GRH levels in various mammals including man (Vrontakis *et al.*, 1991). GAL-is proposed to act at a hypothalamic level in eliciting GH secretion, as the peptide is very effective when injected into the rat third ventricle, but have no effect when added to rat anterior pituitary cells *in vitro* (Ottlecz *et al.*, 1986, 1988).

Aquaculture applications

GH secretion is apparently regulated by several neuroendocrine factors working together. The proposed model summarizes the multifactorial nature of the neuroendocrine regulation of GH secretion in teleost fish (Fig. 1). The growth rate of cultured fish may be stimulated by these neuroendocrine factors added to food, administration of GH or recombinant GH preparations or by feeding the fish with other growth-promoting factors. Feeding or intraperitoneal injection treatment with apomorphine, a dopamine receptor agonist stimulates growth rates of goldfish (Wong *et al.*, 1993a,b). Also a few investigations have evaluated the promising role of human chorionic gonadotropin (HCG) as a growth promoter. Shyama & Keshavanath (1990) have found enhanced growth in silver carp and mahseer, when fed with HCG. HCG and testosterone propionate (TP) in combination were also found to be promising growth stimulant in *Cirrhinus mrigala* (Jayaprakas & Sindhu, 1996).

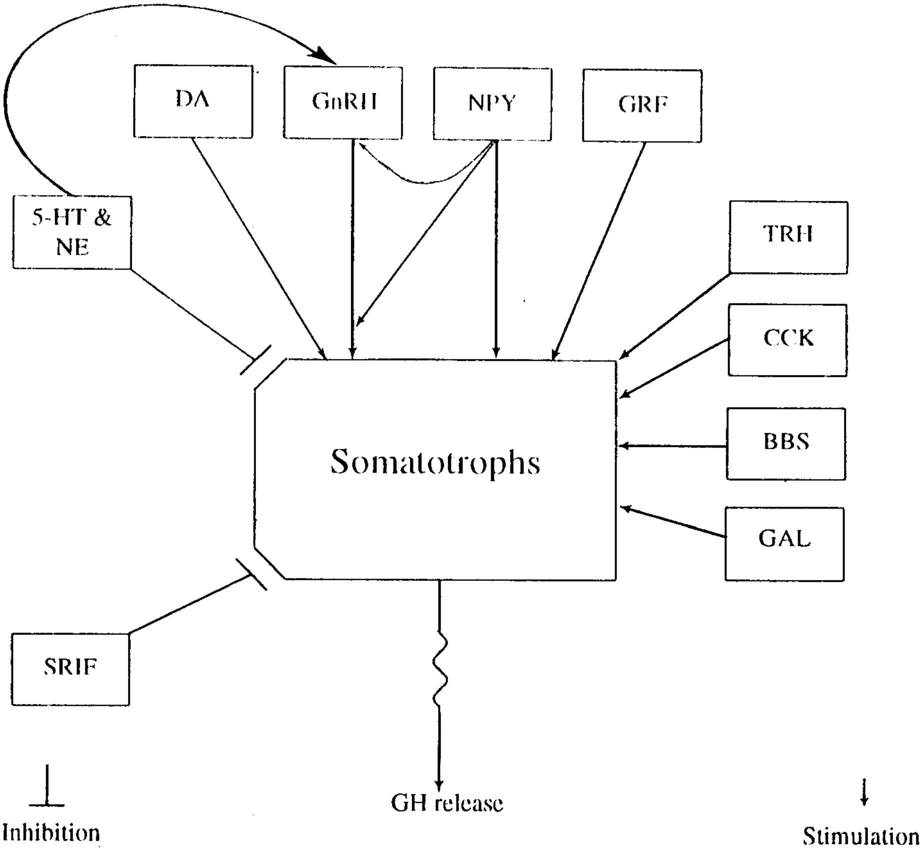

Fig. 1. Model of the multifactorial neuroendocrine regulation of growth hormone (GH) secretion in the teleost fish. Abbreviations : BBS, Bombesin; CCK, Cholecystokinin; DA, Dopamine; GAL, Galanin; GnRH, Gonadotropin-releasing hormone; GRF, GH - releasing factor; 5-HT, Serotonin; NE, Norepinephrine; NPY, Neuropeptide Y; SRIF, Somatostatin; TRH, Thyrotropin-releasing hormone (Peter & Marchant, 1995; after modification).

Oral administration by intubation of recombinant bovine GH to coho salmon stimulates growth rates (McLean *et al.*, 1990). The results do suggest that an oral route is feasible for administration of recombinant GH and other growth-promoting drugs. Growth stimulation following GH administration by injection, oral, rectal, immersion or pellet implantation have been reported in several teleost species in different studies (McLean & Donaldson, 1993). While injection or oral or rectal administration by intubation of GH may be effective in stimulating growth rates of fish under experimental conditions, the necessity of handling individual fish makes this an impractical approach for aquaculture. Addition of a combination of several neuroendocrine factors to food may be a cost-effective means of stimulating growth rates in a wide range of fish species.

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