Growth regulation by growth hormone and insulin-like growth factor-I in teleosts

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Growth hormone (GH) and insulin-like growth factor-I (IGF-I) are polypeptides that play an essential role in the regulation of somatic growth in vertebrates. GH is produced in the pituitary gland and IGF-I is produced mainly in the liver. In teleosts, several aspects on the structure and biological functions of GH and IGF-I have been investigated. Hormonal, nutritional, developmental, and seasonal patterns of GH and IGF-I levels have been examined using homologous assay systems. It has clearly been established that, same as in mammals, the GH–IGF-I endocrine axis plays an important role in the regulation of growth in teleosts.

Key words: growth hormone, growth, insulin-like growth factor, teleost

INTRODUCTION

Growth in vertebrates is under genetic control and is also affected by environmental factors, such as temperature, photoperiod and food availability. The external stimuli and internal physiological conditions are processed and integrated in the brain and relayed to the endocrine organs including the hypothalamus, the pituitary gland, and the peripheral or target organs. The pituitary gland produces growth hormone (GH) that is regulated by hypothalamic hormones such as growth hormone-releasing hormone and growth hormone-inhibiting hormone or somatostatin. GH, released into the bloodstream, binds to its specific receptors in the target organs mainly in the liver, and stimulates synthesis and release of insulin-like growth factor-I (IGF-I). The biological actions of IGF-I are mediated through the IGF receptor. IGF-I circulates in the blood tightly bound to specific binding proteins that differ in site of origin as well as in biological function.

Several aspects on the structure and biological functions of GH and IGF-I in teleosts have been investigated due to their potential use as growth enhancer in aquaculture. Using homologous assay systems, hormonal, nutritional, developmental, and seasonal patterns of GH and IGF-I levels have been examined (see McLean and Donaldson 1993, Björnsson 1997, Duan 1997, 1998, Moriyama et al. 2000). It has been clearly shown that the basic endocrine mechanism underlying growth regulation has been conserved in teleosts relative to the mammalian system (Fig. 1). This paper will focus mainly on the biological function of GH–IGF-I axis in teleostean growth.

TELEOSTS GH AND IGF-I

GH is a single chain polypeptide of about 190 amino acids synthesized by somatotrophs in the anterior lobe of the pituitary gland. In the last two decades, substantial structural information is now available on GH from teleosts by developing protein purification and by employing recombinant DNA technologies. Using homologous GHs, in both purified and recombinant forms, effects has been examined on somatic growth, metabolisms, seawater adapt-

ability involving in seasonal changes during the parr-smolt transformation of salmon, and sexual maturation (see McLean and Donaldson 1993, Björnsson 1997). Sakai et al.(1997) found that salmon GH has immunostimulating effect in salmon. Barrett and McKeown (1988) also reported elevated GH levels in plasma of steelhead trout that were exposed to submaximal training exercise. Taken together with studies in which endogenous GH levels have been measured and correlated with the physiological actions, it is becoming clear that GH is an important and multi-functional hormone in fish.

Insulin-like growth factors, including IGF-I and IGF-II, are single chain polypeptides structurally similar to proinsulin. Both IGF-I and IGF-II are essential for both fetal and postnatal growth in vertebrate animals. The first fish IGF-I cDNA cloned was from coho salmon (Cao et al. 1989). The deduced amino acid sequence of salmon preproIGF-I contains a signal peptide, mature IGF-I, and E-domain, the same as in other vertebrates. Shamblott and Chen (1992) reported the sequence of rainbow trout IGF-II cDNA. Then,
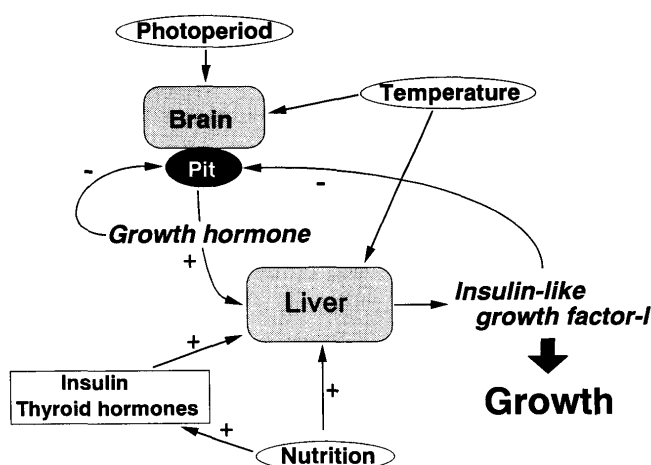
Fig. 1. Endocrine axis controlling growth in teleost fishes. Environmental factors, such as photoperiod and water temperature may stimulate (+) productions of growth hormone (GH) and insulin-like growth factor (IGF-I). Negative feedback (−) of IGF-I inhibits GH secretion by the pituitary gland.

the nucleotide sequence of IGF-I and IGF-II cDNAs has been determined in a number of teleosts (Duan 1998, Moriyama et al. 2000). The amino acid sequence of IGF-I and IGF-II are highly conserved among vertebrates. A wide variety of tissues, such as brain, gill, muscle, kidney, and gut also produce IGF-I locally in teleosts, although liver is the primary site of IGF-I production, same as in mammals (Duan 1997, 1998). IGF-II mRNA is also expressed in multiple tissues in rainbow trout (Shamblott and Chen 1993). IGF-I is involved in the regulation of metabolism in the cells, differentiation and proliferation of the cells, and ultimately body growth. Using a biological assay based on the uptake of ^{35}S-sulfate into the fish branchial cartilage, recombinant coho salmon IGF-I stimulated the sulfate uptake on the cultured branchial cartilage in a dose-dependent manner (Moriyama et al. 1993a, 1997a). The stimulatory effect of salmon IGF-I was similar to that of human IGF-I. Similarly, Upton et al. (1998) reported that piscine and human IGF-Is are equally potent in stimulating protein synthesis in mammalian cells and in binding to the human IGF-I receptors. Taken together, these results indicate that the structure–function relationship of IGF-I have been remarkably conserved among vertebrates.

GROWTH REGULATION BY GH AND IGF-I AXIS

Like in mammals, GH is the primary positive regulator of IGF-I production in teleost fishes. Injection of coho salmon GH to the coho salmon increased the plasma IGF-I and the hepatic IGF-I mRNA levels in a dose-dependent manner (Duan et al. 1993, Moriyama et al. 1994). Likewise, plasma IGF-I levels in rainbow trout were elevated after 12 hr, reaching maximum levels at 24 hr after injection of salmon GH, although plasma GH levels reached to a maximum within few hr (Moriyama 1995). A similar lag time in the elevation of IGF-I after GH treatment has been reported for eels (Duan and Inui 1990). Insulin may also play a role in regulating IGF-I expression and production in salmon. The effect of GH on the hepatic IGF-I mRNA levels in vitro is enhanced by the simultaneous presence of insulin and thyroid hormones (Duan et al. 1992). Injection of streptozotocin, a drug that destroys insulin-producing B cells in pancreas, reduced plasma IGF-I levels and its mRNA levels in the liver (Moriyama et al. 1994, Plisetskaya and Duan 1994). Therefore, insulin may act synergistically with GH to stimulate IGF-I production in salmon.

Treatment of teleost fish with GH and/or IGF-I stimulates somatic growth (McCormick et al. 1992, McLean and Donaldson 1993). There is a high correlation between plasma GH and IGF-I levels and instantaneous growth rate in juvenile salmon (Dickhoff et al. 1997). Beckman et al. (1998) showed that higher plasma IGF-I levels were observed in fast-growing fish than in slow-growing fish. The same authors also reported that plasma IGF-I levels of chinook salmon were higher in warm-water fish than in cold-water fish. These indicate that the changes in GH and IGF-I levels are closely correlated with the growth rate of the fish and reflect the coordination between the endocrine system and physiological responses when environmental cues are changing.

With a view of applying GH to enhance growth in fish,

large number of studies were focused on ways of exogenous GH administration, such as injection, immersion, implantation and oral administration (McLean and Donaldson 1993). Incorporation of GH in food is the most practical and convenient method for a large number of fish in aquaculture. It has been demonstrated that orally administered salmon GH can be transported to the circulatory system as an intact, biologically active hormone, and subsequently improved growth of juvenile rainbow trout (Moriyama et al.1990, 1993b). GH administered to salmonids (100 g body weight) through oral intubation showed its peak in the plasma 15 hr later and remained high for the next several hr (Moriyama 1994). Plasma IGF-I levels on the other hand were elevated within 24 hr after the appearance of the GH peak and remained high for the next few days (Moriyama 1994). These indicate that administration of GH is effective in stimulating IGF-I production and, consequently, fish growth.

The nutritional status has a profound effect on the GH–IGF-I axis in fish. In salmonids, starvation caused cessation of growth but is accompanied by an elevation of plasma GH levels (Moriyama et al. 1994, 1999). The body weight of masu salmon starved for 8 weeks were 2.1 times less than those of the fed fish (Moriyama et al. 1999). The plasma GH and IGF-I levels of these starved fish were 2.9 times higher and 2.1 times lower, respectively, than those of the fed fish. Refeeding of starved masu salmon elevated plasma IGF-I levels, reaching those of fed fish. In coho salmon, starvation also decreased the hepatic IGF-I mRNA levels, and refeeding of the starved fish led to a rise in hepatic IGF-I mRNA (Duan and Plisetskaya 1993). In the gilthead seabream, fasting and feeding, and manipulation of growth rates by ration and protein content of isocaloric diets yielded a good correlation between plasma IGF-I levels and growth rate (Perez-Sanchez et al. 1995). These indicate that this starvation-induced rise in plasma GH levels may be associated with a decrease in the hepatic GH receptor and plasma IGF-I levels and its mRNA expression (Gray et al. 1992, Björnsson 1997).

The release of GH by the pituitary is regulated by hypothalamic hormones, GH-releasing peptide and somatostatin, which inhibits GH release (Luo et al. 1990). IGF-I also inhibits GH release as demonstrated in rainbow trout (Blaise et al. 1995) and the European eel (Huang et al. 1998). In eel, human IGF-I and human somatostatin caused a dose-dependent inhibition of GH release in pituitary cells culture (Huang et al. 1998). In rainbow trout, human IGF-I also inhibited GH release, but was less potent than somatostatin (Perez-Sanchez 1992). An inhibitory effect of human and salmon IGF-Is on GH release in coho salmon was also observed, but was less potent than that of somatostatin (Fig. 2). These indicate that IGF-I inhibits GH release by negative feedback on the somatotropic axis, the same as in mammals (Yamashita 1986). In recent study, it has been reported that ovine GH was decreased GH secretion from perfused rainbow trout pituitaries (Agustsson and Björnsson 2000). It is likely that GH may have a direct negative feedback control on its secretion at the pituitary level.

Anadromous salmonid fishes undergo characteristic parr to smolt transformation (smoltification), which prepares the fish for entry into seawater and for growth and migration to
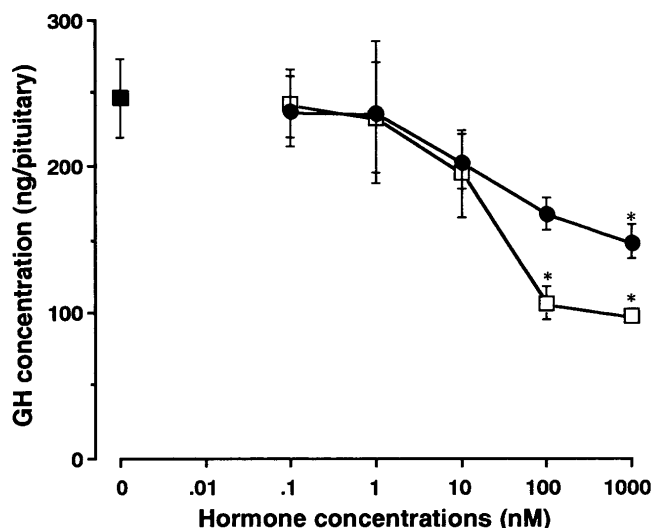
Fig. 2. Inhibitory effects of salmon insulin-like growth factor-I and somatostatin on growth hormone release by salmon pituitary. Symbols represent group as follows: salmon IGF-I (●) and somatostatin (□). Each symbol with vertical bar represents means±SEM.

feeding areas in the ocean. Salmon smoltification is associated with increases in plasma levels of multiple hormones, including GH, thyroxine, cortisol, insulin (Dickhoff et al. 1997), and IGF-I following increases of thyroxine and GH levels (Moriyama et al. 1997b). The hepatic IGF-I mRNA is also elevated following increases of plasma insulin, throxine, and GH levels during salmon smoltification (Duan et al. 1994). IGF-I mRNA levels in the gills were also elevated during smoltification (Sakamoto et el. 1995). Together with previous studies, these results imply that GH - IGF-I axis plays an important role in the regulation of salmon smoltification.

The GH–IGF-I axis may regulate seawater adaptation in some fish species. Plasma levels and turnover rates of GH increased after transfer to seawater in several teleosts (Sakamoto et al. 1993, Mancera and McCormick 1998). The GH occupied and total receptor number in the liver also increases after transfer from freshwater to seawater, indicating the likelihood of at least partial mediation by the liver of the osmoregulatory actions of GH (Gray et al. 1992, Björnsson 1997). IGF-I mRNA expression in the gill also increased after GH injection in salmon and tilapia (Mancera and McCormick 1998, Shepherd et al. 1997). Injection of rainbow trout with IGF-I also enhanced seawater tolerance (McCormick et al. 1991). In the gilthead seabream, however, GH treatment did not increase IGF-I or IGF-II mRNA expression in the gills (Duguay et al. 1996). It is assumed that the osmoregulatory effect of GH may be mediated by IGF-I in salmon.

CONCLUSION

We have observed during the past two decades an increasing body of information on the molecular, biochemical and physiological characteristics of GH and IGF-I in teleosts. This was made possible by improved methods of recombinant DNA technology. As a result, their functions were investigated using homologous assay systems. In teleost fish, GH action on somatic growth is mediated

mainly by IGF-I, same as in mammals. The synthesis and release of GH and IGF-I are regulated by various hormones, nutritional status, some environmental parameters, and the developmental stage of the fish. Although systemic IGF-I is produced mainly in the liver and influenced growth and development in an endocrine fashion, the production of IGF-I in non-hepatic tissues is now well established. The full biological significance of the locally produced fish IGF-I is not clear yet but they are believed to act in an autocrine/paracrine manner.

The identification and characterization of GH and IGF receptors in fish have lagged behind. The structure of GH receptor in fish is yet to be determined, although specific GH binding sites are present in several tissues such as gonads, muscle, cartilage, intestine, posterior kidney and predominantly in the liver. Most recently, a cDNA for IGF/insulin receptor in flatfish has been cloned (Elies et al. 1999). The predicted amino acid sequences of turbot IGF/insulin receptors is similar to the mammalian type I IGF and/or insulin receptor. The cDNA of three forms of IGF/insulin receptors from Japanese flounder were also cloned and sequenced, and appeared to be similar to the mammalian type I IGF and/or insulin receptors (Nakao et al. 1999). Notwithstanding the above studies, a thorough characterization of the IGF/insulin receptors in fish remains to be done and some breakthroughs could be expected in the near future.

ACKNOWLEDGMENTS

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成長ホルモンおよびインスリン様成長因子-Iによる魚類の成長促進

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　魚類の成長促進には，下垂体から分泌される成長ホルモンと肝臓から分泌されるインスリン様成長因子-Iが極めて重要な機能を果たす．過去20年間の研究により，硬骨魚類の成長ホルモンおよびインスリン様成長因子-Iのアミノ酸配列およびcDNAの塩基配列が解析され，また，ホモロガス・ペプチドおよび測定系を用いて，ホルモン投与，栄養状態，発生過程や成長過程および季節変化に伴うこれらホルモンの発現量および分泌量が調べられてきた．その結果，魚類の成長は，哺乳類と同様に，成長ホルモンおよびインスリン様成長因子-Iにより調節されていることが明かとなってきた．本稿では，硬骨魚類の成長促進における成長ホルモンとインスリン様成長因子-Iの生理作用を紹介する．