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The role of growth in endocrine regulation of salmon smoltification

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Growth hormone-insulin-like growth factor I axis

Research during the last decade has clearly established that the major endocrine axis controlling vertebrate growth has been highly conserved during evolution from fish to mammals and birds. The somatomedin hypothesis of Daughaday (Daughaday et al. 1972), proposed to explain a role of growth hormone (GH) in stimulating hepatic production of a factor, somatomedin, to control growth of mammals, applies equally to teleost fish (Komourdjian and Idler 1978; Duan and Inui 1990; Duan and Hirano 1992). Daughday's somatomedin, insulin-like growth factor I (IGF-I), is central to the endocrine axis controlling growth in fish (Fig. 1). The function, structure, and evolution of IGF-I has been reviewed (Bern et al. 1991; Rotwein 1991; Chan et al. 1992; Sakamoto et al. 1993; Siharath and Bern 1993; Duan et al. 1994). The purpose of this paper is to review briefly the function of the endocrine axis controlling the parr-to-smolt transformation (smoltification) of salmonid fishes, and explore how environmental factors, (e.g., photoperiod, temperature, food availability), may influence salmon development through their effects on growth (Fig. 1). The proposed growth influence on salmon smoltification is significant in that the hormones that regulate growth also regulate many of the physiological changes that are characteristic of smoltification (e.g., osmoregulatory mechanisms that promote seawater tolerance).

The liver is probably the major source of IGF-I in salmonid blood, since it has the highest tissue concentration of IGF-I mRNA (Duguay et al. 1994). Furthermore, the administration of GH increases hepatic IGF-I mRNA (Cao et al. 1989; Sakamoto and Hirano 1993; Duan et al. 1994) and elevates blood IGF-I levels (Moriyama et al. 1994). The majority of IGF-I in salmonid blood is probably bound to specific binding proteins (IGFBPs), some of which are influenced by GH, insulin and nutrition (Kelley et al. 1992; Siharath and Bern 1993). The IGFBPs in blood and in tissues surrounding target cells undoubtedly play a significant role in modifying the action of IGF-I in fish, as they do in mammals, although this is largely unexplored in the context of salmon smoltification. IGF-I inhibits GH release by negative feedback, as shown *in vitro* using rainbow trout (*Oncorhynchus mykiss*) pituitary cells (Blaise et al. 1995). In addition to negative feedback, release of GH by the salmonid pituitary may be controlled by both stimulatory (GH-releasing hormone (GHRH), pituitary adenylate cyclase activating polypeptide (PACAP)) and inhibitory (somatostatin-14) hypophysiotropic peptides (Luo et al. 1990; Parker et al. 1997).

Growth rate and IGF-I in fish

Treatment of coho salmon (*Oncorhynchus kisutch*) with IGF-I stimulates growth (McCormick et al. 1992). The role of IGF-I in regulating body growth is supported by the findings that food restriction of rainbow trout reduces hepatic production of IGF-I (Komourdjian and Idler 1978) and hepatic IGF-I mRNA level (Duan and Plisetskaya 1993). Low growth rate of juvenile salmon in seawater is associated with low hepatic IGF-I mRNA (Duan et al. 1995). During the spring, there is a highly significant correlation between

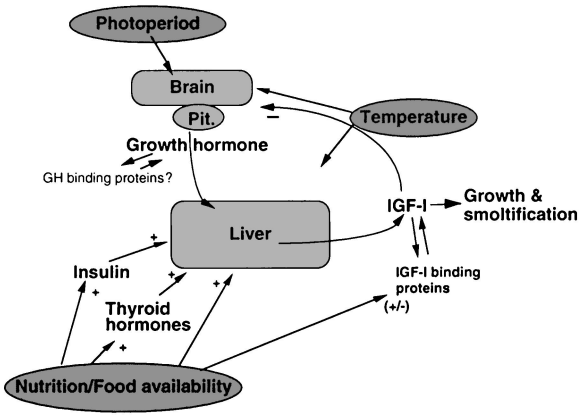

Fig. 1. Endocrine axis controlling growth and smoltification in salmonid fish. Environmental factors may stimulate (+) activity at several points to modify production of insulin-like growth factor (IGF-I). Negative feedback (–) of IGF-I inhibits growth hormone secretion by the pituitary.

plasma IGF-I and instantaneous growth rate of chinook salmon (*Oncorhynchus tshawytcha*) (Beckman et al. unpublished). In gilthead seabream (*Sparus aurata*), fasting and feeding and manipulation of growth rates by ration and protein content of isocaloric diets yield a good correlation between circulating IGF-I and growth rate (Pérez-Sánchez et al. 1994, 1995). These findings indicate that the effects of fasting, ration level and dietary protein on hepatic production of IGF-I in fish is similar to that observed in mammals (Clemmons and Underwood 1991). The mechanism of nutritional effects on hepatic IGF-I production in fish may involve GH receptors (Pérez-Sánchez et al. 1995). GH binding to hepatic cell membranes is reduced in growth-stunted coho salmon (Fryer and Bern 1979; Gray et al. 1990) and during fasting (Gray et al. 1992).

Nutritional regulation of hepatic IGF-I production may involve direct effects of dietary protein or mediation by other hormones. Experimental induction of diabetes by streptozotocin injection of coho salmon reduced hepatic IGF-I mRNA levels (Plisetskaya and Duan 1994). Hepatic production of somatomedin (IGF-I) in starved or hypophysectomized trout is stimulated by treatment with a combination of GH and thyroid hormones (Komourdjian and Idler 1978). The effect of GH on hepatic IGF-I mRNA levels *in vitro* is enhanced by the simultaneous presence of insulin and thyroid hormones (Duan et al. 1992). During smoltification of coho salmon, hepatic IGF-I mRNA levels are significantly correlated with plasma thyroxine (T_4) levels (Duguay et al. 1994).

Photoperiod, growth and salmon smoltification

Salmon smoltification is associated with increases in plasma level of multiple hormones, including GH, T_4, insulin, and IGF-I, among others (Dickhoff 1993) (Fig. 2). It is well established that salmon smoltification and seasonal growth are entrained by changing daylength (Komourdjian et al. 1976a; Hoar 1988). Experimental manipulations of daylength during smoltification influence plasma levels of GH, IGF-I and T_4 (Björnsson et al. 1989; McCormick et al. 1995a,b). The mechanism mediating photoperiodic effects on these hormones most likely involves brain-hypothalamic stimulated release of GH and thyroid stimulating hormone (TSH).

The central role of GH in salmon smoltification is supported by the effect of GH treatment on smoltification and seawater adaptability (Komourdjian et al. 1976b; Clarke et al. 1977; Miwa and Inui 1985; Bolton et al. 1987; Collie et al. 1989). As a major target of GH, elevated plasma IGF-I also has a significant role in seawater adaptability. Injection of rainbow trout with IGF-I enhances seawater tolerance (McCormick et al. 1991) and it is assumed that IGF-I acts, at least in part, on improving the ion transport capabilities of the gill. The osmoregulatory effect of GH may be mediated by hepatic production of IGF-I or by direct action on the gill with or without IGF-I involvement. The levels of gill IGF-I mRNA increase during smoltification of coho salmon (Duguay et al. 1994), and in response to GH (Sakamoto and Hirano 1993). Increased GH or IGF-I may also influence osmoregulatory capacity through their stimulation of cortisol production, which promotes seawater tolerance. Young (1988) has shown that injection of coho salmon with GH enhances the sensitivity of the interrenal to adrenocorticopin, which stimulates cortisol production.

In addition to its effect on osmoregulation, IGF-I may respond to favorable nutritional status and direct growth, which by itself may promote

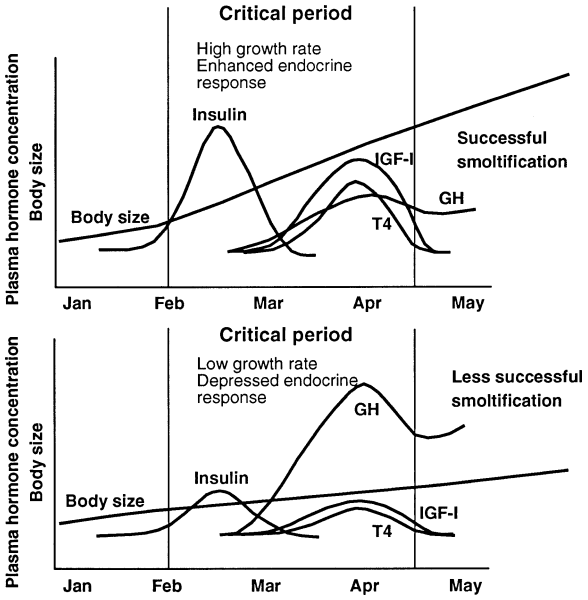

Fig. 2. Diagrammatic representation of plasma hormone levels (insulin, growth hormone (GH), insulin-like growth factor I (IGF-I) and thyroxine (T_4)) and body size during smoltification (critical period). Top graph depicts pattern during high growth rate; lower graph shows pattern during low growth rate.

smoltification. It is generally accepted that large body size of juvenile salmon is important for successful smoltification (Hoar 1988). Successful smoltification is operationally defined here as development of anadromous salmonids that are physiologically ready to migrate downstream, adapt to the ocean environment, and survive to adulthood. Larger smolts within a year class tend to survive to adult at a higher rate than smaller fish (Ward and Slaney 1988; Ward et al. 1989; Henderson and Cass 1991). Large hatchery smolts have relatively greater survival to adult (Bilton et al. 1982; Martin and Wertheimer 1989). Several studies in Atlantic salmon (*Salmo salar*) have found a relation between size of smolts at release and adult return (Virtanen et al. 1991; Farmer 1994). These findings have resulted in a management practice that promotes the release of smolts at a relatively large size (Mahnken et al. 1982). In many studies, substantiating the value of large smolt size, the larger smolts were larger because of recent growth history. Thus, large smolts were also faster growing, so that differences in survival of large and small fish could be due to growth rate, body size, or both factors.

A few studies have noted that growth rate may have a greater influence on smoltification than body size. Wagner et al. (1969) noted that fall chinook salmon exhibiting high growth rates showed better seawater tolerance than larger, slower growing fish. Varnavskiy et al. (1992) measured RNA/DNA as an index of growth rate and found that faster growing coho salmon smolts migrated through the estuary faster than slower growing fish. Dickhoff et al. (1995) showed a relation between spring growth rate of spring chinook salmon smolts for 35 to 44 days prior to release and hatchery return of adults. These studies and others suggest the hypothesis that smoltification may be entrained and stimulated by the combined effect of photoperiod, temperature and nutrition. Increased daylength in the spring, when most salmonids enter smoltification, is often associated with increasing water temperature, increasing food availability and opportunities for growth. These factors may be integrated by the GH-IGF-I axis.

Integration of photoperiod and nutritional control of growth and smoltification

In stunted coho salmon in seawater, pituitary somatotrophs appear more active and plasma GH levels are higher than in faster growing smolts (Clarke and Nagahama 1977; Nishioka et al. 1982; Bolton et al. 1987; Björnsson et al. 1989; Young et al. 1989). Changes in levels of plasma GH, insulin, and hepatic IGF-I mRNA have been documented for fast and slow growing and stunted coho salmon in seawater (Duan et al. 1995). In fast growing fish, plasma insulin and hepatic IGF-I mRNA tend to be higher and plasma GH is lower than in slow-growing and stunted fish. Changes in plasma levels of IGF-I in slow and fast growing chinook salmon during smoltification show higher IGF-I in fast growing fish during the spring months (Beckman, Dickhoff, Larsen, Moriyama and Lee-Pawlak et al., unpublished data). These results demonstrate the combined effects of nutrition (high growth rate) and photoperiodically-entrained elevations in plasma GH and IGF-I. Both fast and slow-growing fish show a seasonal increase in IGF-I production; however, plasma levels of IGF-I and

hepatic IGF-I mRNA levels are lower in slower growing fish.

The positive relationship between growth rate and IGF-I mRNA in liver or plasma IGF-I level contrasts with the negative relation between growth and plasma GH level in slow growing and stunted salmon. These relationships emphasize the importance of hepatic GH receptor level and the negative feedback of IGF-I on pituitary GH production. The dominance of systemic IGF-I negative feedback over hypothalamic hypophysiotropic control of GH production in salmonids was suggested by Blaise et al. (1995).

We propose that growth-controlling hormones integrate photoperiod, temperature and nutritional information and regulate successful smoltification as shown in Figures 1 and 2. Rapidly changing daylength promotes pituitary GH production which stimulates hepatic production of IGF-I. Photoperiod may also mediate increase in plasma thyroid hormone levels through TSH. Increased feeding enhances liver sensitivity to GH through increased GH receptors (among other possible mechanisms). Increased feeding may affect the liver through increasing plasma insulin and/or thyroid hormones, or by direct effects of protein in the diet. As the rate of change in daylength declines approaching summer solstice, the photoperiod-mediated stimulation of GH and T_4 lessens, and their plasma levels begin to decline. Decreases in plasma insulin, thyroid hormones and GH result in a decline in hepatic IGF-I production. Entering summer, insulin, thyroid hormones, and IGF-I have returned to near-basal levels, although plasma growth hormone remains at moderately elevated levels probably due to reduced negative feedback of IGF-I. Increasing temperature during smoltification may result in increased levels of several hormones, particularly T_4 and GH (Björnsson et al. 1989; McCormick et al. 1995), although the interaction of photoperiod and temperature needs further study to separate individual effects.

High growth rate during the spring enhances smoltification by magnifying the photoperiodically induced elevation in IGF-I. Restricted ration or fasting to produce slow growth dampens the photoperiodically induced elevation in IGF-I and retards smoltification. An important question is what minimal growth rate is needed to enhance smoltification. We have seen in juvenile chinook salmon that fish with instantaneous growth rates of 0.2 vs. 0.4% length per day for 2 months is not sufficient to show differences in such smolt indices as gill ATPase activities and plasma T_4 levels (Beckman et al. unpublished data). In another study, we found that differences in instantaneous growth of 0.07 vs. 0.11% length per day for 3 months resulted in significant differences in downstream migration of juvenile spring chinook salmon. Undoubtedly, there is a threshold growth rate that is permissive to successful smoltification; a minimal size is also likely. At very low rates of growth smoltification may be delayed to later in the season or postponed until a subsequent season or year, depending on the species. At higher growth rates smoltification would be promoted. In some species at very high growth rates, reproductive development of males would occur in place of smoltification. It is not clear to us how growth rates affect reproductive mechanisms.

Our hypothetical model of how photoperiod, temperature and nutrition may be integrated to control smoltification is a simplistic, although we think useful model for conceptualizing smoltification and identifying future research priorities. Additional information is needed on IGFBPs, GH binding proteins, receptor regulation, and the involvement of other hormones, e.g., cortisol, and growth factors. Besides the roles of growth regulating hormones in osmoregulatory function, further study should be directed to assess GH and IGF-I effects on morphological and behavioral aspects of smoltification.

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