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Aspects of Salmonid Endocrinology : the Known and the Unknown

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Introduction

Maintenance and improvement of the salmon fishery have been for many years a matter of great concern to Japan on its side of the Pacific Ocean and to Canada and the United States of America on their side. With this concern has come the need to understand the biology of salmonid species, especially of the genus *Oncorhynchus*. In the past 15 years or so, this mutual need of Japanese and North American scientists has brought together for shortterm and longterm collaborations and transpacific exchanges, individuals and laboratories from universities and fisheries agencies concerned with many aspects of salmonid biology. This meeting of Japanese salmon biologists offers an opportunity to present both a survey and a critique of some of the integrated contributions of Pacific Rim scientists and to define the status both of our knowledge and of our lack of knowledge in this field. This essay, intended as a tribute to the value of Japanese-North American scientific interdependence and to the accomplishments of Japanese salmon biologists, will deal with the physiology and especially the endocrinology of salmon as they relate to their development, growth and environmental adaptability. Knowledge of reproductive and migratory biology of these fish has also profitted from transpacific efforts but will not be considered herein. The coverage of the topics selected will necessarily be brief and hence incomplete, and the bibliographic citations relatively minimal. Understandably, most of our attention will be paid to the collaborations between Berkeley and Japanese laboratories. A survey of rainbow trout endocrinology has recently appeared (Bern and Madsen, 1992).

The Endocrinology of Smoltification

The hormonal control of the parr-smolt transformation in salmonids has long been taken for granted (seen Bern, 1978). For many years, thanks to the efforts of William Hoar in Canada and Maurice Fontaine in France, a central role has been ascribed to the thyroid gland. Pigmentation changes accompanying smoltification can be induced by thyroid hormone administration, and it has been an attractive hypothesis to assume that many other structural, functional and biochemical changes seen in the metamorphosis of the parr to the smolt are the direct result of

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thyroid hormone intervention.

Parr and smolt can be distinguished on many bases, in addition to those referred to above. Their osmoregulatory capacities differ, with the parr behaving more as a stenohaline freshwater fish and the smolt showing euryhaline properties (Collie, 1982; Loretz et al., 1982). Intestinal absorption of organic nutrients also differs (Collie, 1985), and carbohydrate and lipid metabolism and its sensitivity to lipotropic factors, including thyroxine, changes with transformation to the smolt stage (Woo et al., 1978; Sheridan et al., 1985; Sheridan, 1986).

The "centrality" of the pituitary-thyroid axis has been supported by the observations by Grau and Dickhoff in the U.S.A. (Grau et al., 1981, 1982; see Dickhoff et al., 1990) and by Yamauchi in Japan (Yamauchi et al., 1985) that blood levels of thyroxine in various *Oncorhynchus* species reach a peak, often associated with the new moon in a spring month, prior to downstream migration. In the amago salmon, blood thyroxine levels increase notably as smolting proceeds (Nagahama et al., 1982). These rises can be interpreted as a time of maximal thyroid stimulation and maximal response to the thyroid hormone. In fact, the high blood levels could mask failure to "use" the hormone and failure to catabolize it (including to convert it efficiently to triiodothyronine, the presumed active form of the hormone). What is still needed here is more information on thyroid hormone kinetics before, during and after smoltification (Specker et al., 1984). Tissue concentrations of thyroxine and triiodothyronine may not reflect blood levels and data on receptor levels in target tissues are minimal. Specker et al. (1992) have recently shown that peaks in tissue concentrations are not in synchrony with peaks in blood concentrations, raising more questions about the physiological meaning of the latter. Nevertheless, the new moon-associated thyroxine peak has provided a valuable and easily recognizable optimal timepoint for release of coho salmon from hatcheries (Nishioka et al., 1989).

During the transfer of young coho salmon from fresh water to seawater, it was discovered in Berkeley that transfer from fresh water to new fresh water (as a control) itself resulted in a significant increase (minor peak) in blood thyroxine levels (Lin et al., 1985). Somewhat later, Yamauchi found that rainfall in a natural stream close to the time of smoltification, caused a peak in thyroxine levels (Yamauchi et al., 1985). These findings led to concern about other environmental factors and to a consideration of the possible synchronization and amplification of thyroxine surges associated with downstream migration by means of the addition of inorganic salts and organic nutrients (Nishioka et al., 1985). The effects of concrete raceways, stored water source, artificial food and continuous lighting of production-oriented California state hatcheries were investigated to ascertain the possible cause of damping of the lunar-phased smoltification-associated thyroid hormone rise. Inasmuch as most hatcheries are associated with hydroelectric dams, reservoir water is supplied to raceways. Few if any of the naturally-occurring changes which happen in a natural stream occur in the raceway. Temperature change, water "quality" changes including turbidity and dissolved solutes, and velocity changes do not occur in the raceways because water is piped in from the reservoir at optimal velocity. The possible effects of these factors are discussed in Nishioka et al. (1985). In addition to unnatural water supply, hatcheries have artificial illumination of the raceways at night. The possible negative effects of continuous illumination (from

overhead lights and improperly shielded ultraviolet water sterilizers) on the lunar-phased smoltification-associated thyroid hormone rise have also been investigated (Nishioka, 1990).

Almost simultaneously with the recognition of an increase in blood thyroid hormone concentration as smoltification proceeded was the delineation of a similar peak in blood cortisol levels (Specker, 1982; see also Young, 1986). Information on the changes of pituitary hormone levels, however, awaited the development of homologous (or semi-homologous) radioimmunoassay systems. For both growth hormone and prolactin assays, several important steps were essential. The hormones needed to be purified in adequate quantities, and this was the critical contribution of the Kawauchi laboratory for both hormones of the chum salmon and of Prunet for prolactin and LeBail for growth hormone from the chinook salmon. Biological testing was also needed and accomplished. To control radioimmunoassays, hypophysectomized salmon were needed. The development of a routine transorbital method of hypophysectomy by Nishioka in Berkeley provided the plasma necessary for validating the specific radioimmunoassays developed by the Hirano laboratory (and by the INRA laboratory at Rennes). Reliable assays for both prolactin and growth hormone became available, and it became possible to integrate the changes in pituitary hormones with the smolting process. Growth hormone rises as smoltification proceeds, and prolactin falls before the time of completion of the process (Young et al., 1989). With the collaboration of Deftos, Björnsson at Berkeley (Björnsson et al., 1989) obtained a seasonal picture of calcitonin levels, and Plisetskaya et al. (1988) at Seattle obtained information on insulin levels. The integrated picture raises some interesting possibilities as to the *sequential* intervention of a variety of hormones in the endocrine control of smoltification. Growth hormone receptor studies have progressed (see below), and pituitary hormone kinetic studies have been initiated (Sakamoto et al., 1990, 1991). The transpacific interaction in the area of pituitary hormone physiology has been remarkably profitable.

The Endocrinology of Osmoregulation

Accompanying the parr-smolt transformation is the transformation of a freshwater-adapted juvenile fish (parr) into a seawater-adaptable stage (smolt). Thus, before migration into seawater can occur, the young salmon must develop the facility to hypoosmoregulate — to cope with the influx of salts from the oceanic environment and the tendency to lose water into this environment.

In salmonids, cortisol, growth hormone (Richman et al., 1987) and insulin-like growth factor-I are all seawater-adapting (the effect of IGF-I was established as the result of a Berkeley-Hirano laboratory collaboration — McCormick et al., 1991), and Lebel and Leloup (1992) have recently found triiodothyronine to be essential in trout for seawater adaptation. On the other hand, prolactin has some action, probably not essential, favoring freshwater adaptation. However, prolactin levels are higher in early stages of smoltification, as would be expected for life in fresh water. Growth hormone and cortisol levels increase as the time for successful smoltification and seawater entry approaches, and prolactin levels subside (Young et al., 1989). In those euryhaline teleosts which have been analyzed experimentally,

prolactin is essential for hyperosmoregulation in fresh water; cortisol aids in seawater adaptation, but no osmoregulatory role for growth hormone has yet been clearly established in species other than salmonids. In salmonids, a fascinating problem for the future concerns the apparent disjunction between the growth effects and the osmoregulatory effects of both growth hormone and IGF-I.

Salmonids are distinctive in their response to hypophysectomy: they can survive relatively well in the absence of the pituitary when transferred to fresh water; however, hypophysectomized coho salmon die within a few days after transfer to seawater (Nishioka et al., 1987; Yamauchi et al., 1991). This is the converse of the situation typical of euryhaline teleosts, and may reflect the relative importance of prolactin and growth hormone in salmonid physiology. In a recent study by Madsen and Bern (1992), prolactin had no osmoregulatory effect by itself in freshwater- or seawater-adapted trout; yet it significantly antagonized the hypoosmoregulatory effects of growth hormone.

McCormick first cultured gill filaments of coho salmon and found that the only hormone that directly stimulated Na^+ , K^+ -ATPase activity *in vitro* was cortisol (McCormick and Bern, 1989). However, recently Madsen (1992, personal communication; Madsen and Bern, 1991) has found that IGF-I may also act directly *in vitro* depending on the stage of smoltification. Thus, early in the parr-smolt transformation, gill filaments are insensitive to IGF-I *in vitro*. Growth hormone injection at this time induces sensitivity to IGF-I, and this sensitivity is seen later in development in untreated fish (near the peak of smoltification) when endogenous growth hormone levels are increasing. After smoltification, sensitivity to IGF-I is lost, even in growth hormone-treated fish. These findings suggest a parallel to the dual effector hypothesis of growth hormone action suggested for cartilage growth (see below). Seasonal (smoltification-associated) changes in sensitivity to cortisol have also been found in a collaboration between our laboratory and the Dickhoff laboratory (McCormick et al., 1992a). In another collaboration between our laboratory and the Hirano laboratory (McCormick et al., 1992b), the opercular membrane was found to be a site of calcium uptake in rainbow trout.

Iwata developed the method of transepithelial potential measurement at Berkeley, as a means of studying the osmoregulatory capacity of the entire fish. First used by him on a goby, the technique enabled him to follow the changing patterns during coho salmon smoltification (Iwata et al., 1987b). The method was later used in Berkeley to study hormonal effects on osmoregulation in the tilapia, a real and continued contribution of transpacific collaboration. Iwata also discovered at Berkeley that the development of ocular (lens) cataract on transfer of coho from fresh water to seawater was an indication of unreadiness for seawater entry (Iwata et al., 1987a). Salinity preference studies occurred as a result of application of methods developed by Iwata at Otsuchi to coho salmon in collaboration with Yamauchi at Berkeley (Iwata et al., 1990).

Both the Hirano laboratory (Suzuki, Yada) and the Bern laboratory (Kelley, Nishioka) have been concerned with the possible effects of osmotic pressure on the release of the two osmoregulatory hormones: growth hormone and prolactin from incubated chum salmon and rainbow trout pituitaries, and coho salmon pituitaries, respectively. Unlike conclusions from the study of certain euryhaline species, the consensus from the studies conducted on both sides of the Pacific (information has

been actively exchanged) is that pituitary cell function in salmonids is little affected by changes in osmotic pressure occurring within the physiologically significant range (see Gonnet et al., 1988; Nishioka et al., 1988; Kelley et al., 1990, 1992).

The Endocrinology of Growth

The simplistic statement that growth in fishes is controlled by growth hormone from the pituitary needs considerable amplification. In the first place, growth hormone does not act primarily on growing structures such as cartilage (bone) but rather induces the liver to secrete insulin-like growth factor(s) (IGFs: somatomedins) which directly stimulate chondrogenesis. Chondrogenesis and osteogenesis involve a series of phases, including chondrocyte proliferation, differentiation and function (chondroitin sulfate matrix deposition), transformation into osteocytes, and bone deposition and turnover. These phases may be differentially influenced by various controlling factors, including the local production of some agents (especially IGF-I), and a variety of autocrine and paracrine mechanisms may be involved (extrapolating from studies on mammals).

The present interest in the role of IGF-I was sparked by Duan working with Inui and Hirano. Their important findings on the eel stimulated experiments by McCormick and others (1992c, d) in Berkeley on the effects of recombinant bovine IGF-I (Monsanto) on growth in the coho salmon (see Bern et al., 1991). rbIGF-I is remarkably effective in fishes, reflecting the high homology between the coho salmon and the bovine/human genes (Cao et al., 1989). Sulfate incorporation into chondroitin sulfate and thymidine incorporation into DNA can be employed simultaneously in the study of cartilage responses to hormonal manipulations *in vivo* and *in vitro* (P. Tsai et al., in preparation). A working hypothesis for the control of coho salmon growth proposes that growth hormone stimulates hepatic IGF-I secretion and sensitizes prechondrocytes to its action; this is the "dual effector" hypothesis of Green et al. (1985). The detailed picture still must be delineated by further study; in particular, possible interactions of growth hormone and IGF-I with insulin, thyroid hormones, and cortisol at the target level as well as on the liver need analysis. A possible role of prolactin in juvenile (pre-parr) salmon needs investigation. In addition, the participation of IGF-binding proteins in facilitating and inhibiting cartilage responses must be considered. The three principal mammalian IGF-binding proteins (1, 2 and 3) appear to have their counterparts in the blood of teleosts, including coho salmon; their electrophoretic characteristics and their physiological responses in teleosts to date parallel those in mammals (Kelley et al., 1992).

Growth hormone receptor studies have been conducted on coho salmon by Gray in the Bern laboratory (Gray et al., 1990) and on rainbow trout by Sakamoto in the Hirano laboratory (Sakamoto and Hirano, 1991; see also Yao et al., 1991). Crucial to the accurate measurement of growth hormone receptor levels was the $MgCl_2$ method for removing endogenous growth hormone bound to receptors, as used by Sakamoto and Hirano and communicated to Gray. Both the pituitary and nutrition appear to regulate hepatic growth hormone receptors in coho salmon. Receptors in salmon fasted for three weeks were decreased by 35-40% relative to fed fish. However, refeeding of fasted salmon for one week increased hepatic growth

hormone receptors to significantly higher levels than in fasted or fed fish. Pituitary regulation of salmon growth hormone receptors is indicated, as receptors were decreased following hypophysectomy. Acute treatment with growth hormone reduced growth hormone receptor levels, but effects of chronic growth hormone have not been reported to date. Treatment with insulin-like growth factor-I, thyroxine, or cortisol appeared to be without effect on hepatic growth hormone receptors in salmon (Gray et al., 1992a, b).

Attempts have been made — and will continue to be made — to produce transgenic trout and other salmonids, using growth hormone transgenes. Whether one will obtain profitably larger fish which are palatable and nutritious, only time and considerable effort will reveal. However, regardless of the immediate practical outcome, fish physiologists, biochemists and molecular biologists agree that much can be learned from such transgenic animals, especially in regard to physiological mechanisms and pathological processes. Fish bearing growth hormone transgenes have to be considered from aspects other than increased size, body weight and muscle mass. In salmonids, growth hormone favors salt excretion and water retention, which are not assets in the freshwater environment in which presmoltifying salmon develop. Excess growth hormone is potentially diabetogenic, both because of direct metabolic action and because of adrenocorticotrophic activity (favoring higher levels of cortisol, a gluconeogenic factor). Growth hormone also favors the conversion of thyroxine to triiodothyronine, the active form. In addition, this multivalent hormone may have important immunological and reproductive effects. Furthermore, analytical studies on fish indicate that growth hormone may favor the down-regulation of its own hepatic receptors in the short term (longterm effects are not known, but chronic growth hormone exposure could be self-defeating as a growth stimulant if insulin-like growth factor production is reduced thereby) (see Bern, 1990). IGF-I transgenes may prove even more useful than growth hormone transgenes.

The Endocrinology of Stunting

In coho salmon, the phenomenon of “stunting” has been recognized for some years (see Bern, 1978). It is important to point out that although stunts are small and often immature (parr-like) in appearance, they survive under laboratory/net pen conditions when transferred to seawater. They do not grow, however, in this environment. It might be predicted that these fish would be deficient in growth hormone, especially as they are largely panhypoendocrine, except for the corpuscles of Stannius (Aida et al., 1980). Initially, this generally panhypoendocrine status was recognized on the basis of histological and cytological criteria by Nishioka (Nishioka et al., 1982) and by Nagahama who collaborated with both Nishioka and Clarke (Clarke and Nagahama, 1977). However, unexpectedly active-appearing growth hormone cells were noted in the pituitary. With the development of a radioimmunoassay for salmon growth hormone, it was established that stunts had significantly higher levels of growth hormone than did normal smolts in seawater (Bolton et al., 1987). Both Atlantic salmon stunts in seawater net pens (Björnsson et al., 1988) and natural stunts in Siberian waters (Varnavsky et al., 1992) also show blood plasma growth hormone levels appreciably higher than normal. The informa-

tion on natural stunts confirming the consistency of high growth hormone levels is the result of a Japanese-Russian collaboration, and these data are especially valuable.

The failure to grow in the presence of an excess of growth hormone suggests that there may be a deficiency in the mediation of growth hormone action on bone growth (that is, chondrogenesis) by insulin-like growth factor-I. Either the growth hormone receptors in the liver are low in number or defective in further signalling and/or the insulin-like growth factor-I receptors in cartilage are deficient. A small amount of data (K.M. Kelley, 1991, personal communication) indicates that sulfate uptake by cartilage is lower in stunts, suggesting insulin-like growth factor-I deficiency. A comparison of the response of cartilage from stunts and smolts to insulin-like growth factor-I *in vitro* would be informative. However, no work has yet been done with insulin-like growth factor-I receptors in any teleost species, and stunts have never been treated *in vivo* with insulin-like growth factor-I to see if they are responsive.

When coho stunts are returned to fresh water for three weeks, growth hormone levels in the blood fall dramatically, and other hormone levels become similar to those of normal smolts similarly transferred (Young et al., 1989). Stunted salmon have lower hepatic growth hormone receptor levels than do normally-growing seawater salmon (Gray et al., 1990). Growth hormone receptors increased approximately two-fold among stunts transferred to fresh water, but remained low if these fish were not fed after transfer. These observations on growth hormone receptor regulation in stunts are consistent with the theory that stunt pathology is related to poor feeding following premature transfer to seawater (Gray et al., 1992b).

The Endocrinology of Embryonic Development

One of the newest areas of research in developmental endocrinology concerns the presence of hormones and hormone-like growth factors in eggs. Either the hormone itself or the mRNA for a peptide hormone may be transferred from the female fish to eggs undergoing maturation in the ovary. After discovery of appreciable amounts of thyroxine in coho salmon eggs in the Bern laboratory (Kobuke et al., 1987; Greenblatt et al., 1989) and the Hirano laboratory (Tagawa and Hirano, 1987), studies in both laboratories confirmed the existence of thyroxine and triiodothyronine in a number of teleost species (Brown et al., 1987; Tagawa et al., 1990). At the same time, the Hirano laboratory improved the technology for assaying thyroid hormones from eggs, larvae and tissues, greatly contributing to further studies including those of our laboratory both on salmonids and on other teleosts. Teleosts appear to vary in the influence of egg (maternal) thyroid hormones in larval and subsequent development. The major impact of the discovery of their occurrence, however, was the recognition that the sexually maturing female fish can contribute to its vitellogenic oocytes a variety of factors possibly important in development, including sex differentiation. A new concept in embryology is emerging: the "endocrinization of the early embryo" (de Pablo and Roth, 1990; see also Brown and Bern, 1989; Bern, 1990).

In teleosts, data exist for the occurrence in eggs not only of thyroid hormones but also of sex steroid and corticosteroid hormones of maternal origin (e.g., see de

Jesus and Hirano, 1992). Extrapolating from other vertebrate studies, similar transfer of insulin, growth factors (such as TGF β and FGF), activins, catecholamines and various neurotransmitters can be expected, and research seeking to identify other agents (pituitary hormones, other growth factors, etc.) is warranted. The technology for identifying small amounts of peptides and proteins in the presence of confounding quantities of yolk proteins and lipids is a challenge in itself. TGF β , FGF and especially activin A (EDF) have proven to be effective inducers of mesoderm in amphibian embryonic development.

Other Aspects of Salmonid Endocrinology

Time and space do not permit a broader discussion of Japanese-North American interactions in the area of salmonid endocrine physiology. Recognition should justifiably be paid to such important collaborations as those listed hereunder: (1) between the Kawauchi laboratory at Kitasato University and the W. Dickhoff-P. Swanson-E. Plisetskaya laboratory at the University of Washington at Seattle, on the biological characterization of salmon pituitary hormones; (2) among Y. Nagahama of Kiseiken at Okazaki, W.C. Clarke at the Pacific Biological Station at Nanaimo, and W.S. Hoar at the University of British Columbia, on salmon pituitary cytophysiology; (3) between the T. Hirano laboratory at Tokyo University's Kaiyoken and Clarke on the role of growth hormone in seawater adaptation of juvenile salmon; (4) between the Nagahama laboratory and the E.M. Donaldson group at the West Vancouver Laboratory on the salmonid aromatase transgene; (5) among M. Nozaki of the Primate Research Institute at Inuyama and A. Gorbman and Plisetskaya at the University of Washington and other colleagues, on hormone immunocytochemistry of the salmonid pancreatic islet; (6) between Gorbman and a series of Japanese investigators (K. Oshima, K. Ueda, T. Hara, H. Shimada, and G. Hoshiai) on olfaction and salmonid migration and the effect of thyroid and steroid hormones on brain electrophysiology; (7) between A. Hara of the Nanae Station of Hokkaido University and C. Sullivan at North Carolina State University at Raleigh on salmonid vitellogenesis and the transport role of vitellogenin; (8) among K. Yamauchi and K. Soyano of the Hokkaido University Faculty of Fisheries, and Hara, Nagahama and Sullivan, on the role of thyroid hormones in trout oocyte maturation.

Conclusions

This brief survey, despite its Berkeley-centricity, makes clear how meaningful transpacific contacts have been in the acquisition of the considerable information we now have on the endocrinology of developing salmon. At the same time, it is evident that major gaps in our knowledge still exist. It is to be hoped that other collaborations and exchanges of scientists will help fill these gaps in the future and continue the tradition so well justified by past accomplishments.

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