Osmoregulatory actions of growth hormone and its mode of action in salmonids: A review

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Abstract

Osmoregulatory actions of growth hormone (GH) and its mode of action in salmonids are reviewed. We present evidence suggesting that insulin-like growth factor I (IGF-I) mediates some of the actions of GH on seawater acclimation. Plasma concentration and turnover of GH rise following exposure to seawater. Exogenous GH (*in vivo*) increases gill Na^+,K^+-ATPase activity and the number of gill chloride cells, and inhibits an increase in plasma osmolarity and ions following transfer of fish to seawater. A single class of high affinity GH receptors is present in the liver, gill, intestine, and kidney. The levels of IGF-I mRNA in the liver, gill and kidney increased after GH-injection. After transfer to seawater, IGF-I mRNA increased in the gill and kidney following the rise in plasma GH, although no significant change was seen in the liver. Injection of IGF-I improved the ability of the fish to maintain plasma sodium levels after transfer to seawater. GH treatment also sensitizes the interrenal to adrenocorticotropin (ACTH), increasing cortisol secretion. Both cortisol and IGF-I may be involved in mediating the action of GH in seawater adaptation, although studies on the effect of GH on osmoregulatory physiology of non-salmonid species are limited. An integrated model of the osmoregulatory actions of GH is presented, and areas in need of research are outlined.

Résumé

Cet article est une revue des effets osmorégulateurs de l'hormone de croissance et de son mode d'action. Nous présentons des résultats qui suggèrent que le facteur de croissance de type insuline (IGF-I) est un médiateur de certaines des actions de la GH sur l'adaptation à l'eau de mer. Les concentrations plasmatiques et le renouvellement de la GH augmentent après transfert en eau de mer. La GH exogène stimule (*in vivo*) l'activité Na^+,K^+-ATPase et le nombre de cellules à chlorure branchiales et inhibe les augmentations de l'osmolarité et des concentrations ioniques du plasma observées après transfert en eau de mer. Une seule classe de récepteurs à haute affinité pour la GH est présent dans le foie, les branchies, l'intestin et le rein. Les niveaux d'ARNm d'IGF dans le foie, les branchies et le rein augmentent après injection de la GH. Après transfert

en eau de mer, les ARNm de l'IGF augmentent dans les branchies et dans le rein en suivant l'augmentation de GH plasmatique, bien qu'aucune modification ne soit observée au niveau du foie. L'injection d'IGF augmente la capacité du poisson à maintenir ses niveaux de sodium plasmatique après transfert en eau de mer. Le traitement à la GH augmente la sensibilité à l'adrenocorticotropine (ACTH) et stimule donc les niveaux de cortisol. A la fois le cortisol et l'IGF-I semblent impliqués comme médiateurs des effets de la GH dans l'adaptation à l'eau de mer, bien que les études sur les effets de la GH sur la physiologie de l'osmorégulation chez les espèces non-salmonidés restent encore limitées. Un modèle intégré des actions de la GH sur l'osmorégulation est présenté et les domaines de recherche à développer sont soulignés.

Introduction

Although prolactin (PRL) has been referred to as the most versatile of pituitary hormones, there is substantial evidence indicating that one of its major functions throughout the vertebrates is to control fluid dynamics. In fishes, PRL is important in maintaining ion balance in fresh water (Brown and Brown 1987; Hirano *et al.* 1987). Interestingly, there is recent evidence that gwoth hormone (GH), closely related to PRL in its amino acid sequence, facilitates seawater acclimation in several salmonid species, in addition to its action on growth promotion. Smith (1956) first reported that brown trout treated for 2 weeks with mammalian GH survived the transition from fresh water to seawater better than controls. Komourdjian *et al.* (1976), Clarke *et al.* (1977) and Miwa and Inui (1985) confirmed the effect of GH in other salmonids. These effects could be consequences of growth-promoting actions of GH since salinity tolerance of most salmonids is size-dependent (reviewed by McCormick and Saunders 1987; Hoar 1988). However, in short-term (7-day) experiments on unfed rainbow trout, Bolton *et al.* (1986) found effect of GH on salinity tolerance without any significant weight changes. Homologous GH lowered plasma ions in rainbow trout transferred to seawater, whereas salmon PRL caused an increase; therefore the action of GH on seawater acclimation is specific to GH.

In this paper, we review the osmoregulatory actions of GH and its mode of action in salmonids, presenting new evidence that insulin-like growth factor I (IGF-I) likely mediates actions of GH on seawater acclimation. We are focusing on salmonids, because little is known about osmoregulatory effects of GH in non-salmonid fishes. We propose a model for the osmoregulatory actions of GH in salmonids. Intriguing topics for future research are also discussed.

Response of growth hormone to osmotic stimulation

Many salmonid species migrate to the sea after parr-smolt transformation. Patterns of the smolt transformation vary by salmonid species (Hoar 1988). The pink salmon is already silvery and able to enter seawater as emerging fry. Some species of *Salvelinus* migrate only short distances into the sea for a few months. The rainbow trout (sedentary strain), brown trout (sedentary strain), lake char and whitefish (*Coregonus*) are not known to smolt or enter the sea at all. Most species of *Oncorhynchus* and *Salmo* are intermediate between these extremes and spend 1–3 or more years in fresh water before smolting. Plasma GH levels are elevated during smoltification in coho, Atlantic, and masu salmon (Sweeting *et al.* 1985; Björnsson *et al.* 1989; Boeuf *et al.* 1989; Okumoto *et al.* 1989; Prunet *et al.* 1989; Young *et al.* 1989a; McCormick and Björnsson 1993). According to Varnavsky *et al.* (1992), plasma GH concentrations were higher in wild coho salmon smolts caught at the river mouth than in the parr caught in the river. Elevated GH levels presumably reflect developmental and osmoregulatory changes during smoltification, migration, and entry into seawater. Exposure of coho salmon, chum salmon, Atlantic salmon, and rainbow trout to seawater increases (transient) circulating GH levels (Sweeting *et al.* 1985; Hasegawa *et al.* 1987; Sweeting and McKeown 1987;

Ogasawara *et al.* 1988; Björnsson *et al.* 1989; Boeuf *et al.* 1989; Collie *et al.* 1989; Young *et al.* 1989b; Sakamoto *et al.* 1990, 1991; Sakamoto and Hirano, 1991, 1993; Yada and Hirano 1992). No significant change or decrease in plasma GH occurred when chum salmon and coho salmon were transferred from seawater to fresh water (Bolton *et al.* 1986; Hasegawa *et al.* 1987; Ogasawara *et al.* 1989; Hirano *et al.* 1989; Young *et al.* 1989b; Sakamoto *et al.* 1991). However, the plasma GH level does not always increase after acclimation to seawater or during the parr-smolt transformatin of salmonids; no change was seen in coho salmon, Atlantic salmon, or amago and sockeye salmon (Clarke *et al.* 1989; Young *et al.* 1989a; Rydevik *et al.* 1990; Yada *et al.* 1991, 1992). Yada *et al.* (1991, 1992) and Björnsson *et al.* (1989) demonstrated in amago and sockeye salmon and Atlantic salmon that the response of GH is related to the development of preparatory mechanisms for seawater entry. Stress such as handling and hypoxia also affects the levels of circulating GH (see Pickering *et al.* 1991 for review). Because plasma concentrations of the hormone are the results of an equilibrium between the pituitary secretion rate and metabolic clearance rate, a complete assessment of GH dynamics requires kinetic study.

The metabolic clearance rate and the calculated secretion rate of GH increased after transfer of rainbow trout and coho salmon to seawater (Sakamoto *et al.* 1990, 1991). When coho salmon were transferred from seawater to fresh water, GH kinetics did not change (Sakamoto *et al.* 1991). GH synthesis *in vitro* increased after acclimation to seawater in coho salmon (Kelley *et al.* unpublished data), but not in rainbow trout (Yada and Hirano 1992). Yada *et al.* (1992) also demonstrated in amago salmon that response of pituitary GH mRNA to seawater exposure is related to the development of preparatory mechanisms for seawater entry. In kokanee salmon and chum salmon (Leatherland and McKeown 1974; Suzuki *et al.* 1987), changes in GH secretion were not detectable *in vitro* in response to changes in medium osmotic pressure. In rainbow trout and coho salmon, *in vitro* secretion of GH was inhibition only after a large increase in the sodium content of the ambient medium (Baker and Ingle-

ton 1975; Kelley *et al.* 1992). Thus, changes in extracellular osmolarity within physiological ranges do not seem to affect GH release directly in salmonids (see also Sweeting and McKeown 1987). However, cortisol stimulates GH release in another euryhaline teleost species, the tilapia (Nishioka *et al.* 1985; Helms *et al.* 1987). Several studies demonstrated that plasma cortisol levels increase when euryhaline teleosts (including salmonids) are transferred to seawater (Balment *et al.* 1987; Young *et al.* 1989a,b; Sakamoto and Hirano 1991). Whether cortisol stimulates GH release in salmonids is not yet known. The bulk of evidence from *in vivo* mammalian studies suggests that corticosteroids suppress GH levels although their actions are complex and biphasic, with both stimulatory and suppressive components (Ceda *et al.* 1987; Casanueva *et al.* 1988). On the other hand, the changes in metabolic clearance rate of GH during acclimation to seawater may largely reflect altered physiological use of the hormone, such as binding to receptors.

In vivo effects of growth hormone on osmoregulation

Some information on *in vivo* effects of GH has been available to assess the sites and mechanisms of GH's osmoregulatory actions in salmonids (Table 1). In rainbow trout and brown trout, GH injections inhibit the increase in plasma ion (Na^+, Mg^{++}, Ca^{++}) levels in seawater-challenge tests (Bolton *et al.* 1987; Collie *et al.* 1989; Madsen and Bern 1992). Whereas the reduction in plasma Na^+ after GH treatment implicates the gill and the gut as major sites of monovalent ion transport, changes in Mg^{++} and Ca^{++} levels may indicate actions on the kidney. Treatment of several salmonid species with GH increased gill Na^+,K^+-ATPase activity and/or chloride cell development (Table 1). Bovine GH stimulates Na-dependent proline absorption in coho salmon intestine. These results indicate the gill, gut, and kidney as potential targets of GH osmoregulatory action.

GH may also influence acclimation to seawater indirectly through effects on energy metabolism. As in mammals, GH seems to have lipolytic, dia-

Table 1. In vivo effects of growth hormone treatment on osmoregulatory mechanisms in salmonids.

Effects	Species	References
↓ Plasma Na$^+$, Cl$^-$ osmolarity	sockeye salmon	Clarke *et al.* 1977[a]
	amago salmon	Miwa and Inui 1985[a]
	rainbow trout	Bolton *et al.* 1987[b]; Collie *et al.* 1989; Madsen 1990b; McCormick *et al.* 1991b; Madsen and Bern 1992
	Hx coho salmon	Richman *et al.* 1987
	brown trout	Madsen 1990c; Madsen and Bern 1992
	Atlantic salmon	Boeuf *et al.* 1990; McCormick, unpublished
↓ Plasma Ca^{++}/Mg^{++}	rainbow trout	Bolton *et al.* 1987[b]; Collie *et al.* 1989
	brown trout	Madsen and Bern 1992
↑ Gill Na$^+$,K$^+$-ATPase	amago salmon	Miwa and Inui 1985[a]
	coho salmon	Richman and Zaugg 1987[a]?
	Hx coho salmon	Björnsson *et al.* 1987
	rainbow trout	Madsen 1990b; Madsen and Bern 1992
	brown trout	Madsen 1990c
	Atlantic salmon	Boeuf *et al.* 1990; McCormick, unpublished
Chloride cells (size/density)	rainbow trout	Madsen 1990b
	brown trout	Madsen 1990c
↑ Intestine proline absorption	coho salmon	Collie and Stevens 1985[a]

[a]Effects could be consequences of growth-promoting actions of growth hormone;
[b]Effects were studied with homologous hormons. Hx, hypophysectomized.

betogenic, and protein-anabolic effects in salmonids (McKeown *et al.* 1975; Higgs *et al.* 1976; Markert *et al.* 1977; Sweeting *et al.* 1985; Sheridan 1986, 1988). Thus, GH may help fuel any potential increase in energy requirements during seawater acclimation.

Because of the limited research into these effects of GH in salmonids *in vitro*, it is difficult to distinguish between direct and indirect effects on any particular target.

Growth hormone receptors: Characterization and response to seawater

To assess the target organs for GH in salmonids, a homologous radioreceptor assay for GH was established for coho salmon and rainbow trout (Gray *et al.* 1990; Sakamoto and Hirano 1991; Yao *et al.* 1991). GH receptors were observed not only in the liver but also in the gill, intestines, and posterior kidney of the trout. Scatchard analyses of the binding in these tissues point to the presence of a single class of GH-specific receptors, characterized by high affinity ($K_a = 2-3 \times 10^9$/M) and low capacity ($N_{max} = 1-100$ fmol/mg protein). The capacity of receptors in the gill, intestine and kidney was about 3–6% of that in the liver (Sakamoto and Hirano 1991). These results indicate that liver and osmoregulatory organs are potential primary targets of GH action.

Free binding sites for GH in the liver decreases after transfer to seawater; binding in the gill and kidney was not altered significantly. MgCl$_2$ treatment to remove bound GH from the receptors indicated that the reduction in the liver binding is probably the results of receptor occupancy by increased endogenous GH. The occupied and the total (MgCl$_2$-treated) receptor numbers in the liver increased after transfer, indicating the likelihood of at least partial mediation by the liver of the osmoregulatory actions of GH (Sakamoto and Hirano 1991). An interaction of one or more factors, such as hormones (*e.g.*, GH, thyroid hormones and cortisol) and nutrition, with GH receptor numbers may occur and contribute to the accli-

mation of salmonids to the marine environment (see Kelly *et al.* 1991; Mori *et al.* 1992; Gray *et al.* 1993).

Hormonal mediators of osmoregulatory actions of growth hormone

Cortisol

Cortisol is also an important hormone in teleost osmoregulation. In a variety of teleosts, *in vivo* treatment with cortisol stimulated ion pumps in the gill, intestines, kidney, and urinary bladder, as reflected in increased Na^+,K^+-ATPase activity or fluid transport (Mayer and Maetz 1967; Pickford *et al.* 1970; Hirano and Utida 1971; Foskett *et al.* 1983; Veillette *et al.* 1991). Cortisol is especially important in acclimation to seawater by stimulation of gill Na^+,K^+-ATPase activity and chloride cell differentiation in several salmonid species (Björnsson *et al.* 1987; Richman and Zaugg 1987; McCormick and Bern 1989; Bisbal and Specker 1991; Madsen 1990a,c). Higgs *et al.* (1977) showed that GH increased the interrenal nuclear diameter of coho salmon, and Young (1988) found that GH, either *in vivo* or *in vitro*, enhanced the response of coho salmon interrenal to adrenocorticotropin (ACTH), increasing cortisol production.

Thyroid hormones

Thyroid hormones have been hypothesized to play a role in many developmental processes including that of hypoosmoregulatory mechanisms (see Hoar 1988). There is little data, however, unequivocally demonstrating an effect of thyroid hormones on osmoregulatory processes. Lebel and Leloup (1992) have recently shown that conversion of T_4 to T_3 is necessary for the development of mechanisms for seawater osmoregulation in rainbow trout. Although relatively little is known of the functional relationship between GH and thyroid hormones the stimulation of hepatic T_4 deiodination by GH has been reported in rainbow trout (MacLatchy and Eales 1990; MacLatchy *et al.* 1992).

IGF-I

As in higher vertebrates, the effects of GH on skeletal growth of fishes are mediated largely by liver-produced IGF-I, supporting a somatomedin hypothesis (see Bern *et al.* 1991). Induction of IGF-I mRNA in the liver, gill, and body kidney after GH treatment of coho salmon and rainbow trout revealed that the regulated expression of the IGF-I gene by GH is presented already in salmonid fishes (Cao *et al.* 1989; Sakamoto and Hirano 1993).

IGF-I can improve the ability of rainbow trout and Atlantic salmon in 33% seawater to maintain plasma osmolarity and sodium levels after transfer to seawater (McCormick *et al.* 1991; McCormick, unpublished). IGF-I mRNA level was not altered significantly in the liver after transfer of rainbow trout to seawater, but increased in the gill after 1 day and in the kidney after 8 days, subsequent to a rise in plasma GH (Sakamoto and Hirano 1992). These results suggest that locally expressed IGF-I mediates the effect of GH on seawater acclimation. Pretreatment of coho salmon with GH results in increased sensitivity of the isolated gill filament to IGF-I in stimulating Na^+,K^+-ATPase *in vitro*, although IGF-I itself was not effective (Madsen and Bern 1991). In this context, GH may stimulate differentiation of chloride cells through local production of IGF-I, whereas systemic IGF-I may act largely on the differentiated cells. This is similar to the dual effector model for the promotion of growth by GH in mammals (Green *et al.* 1985) and fish (Gray and Kelley 1991), in which GH is hypothesized to stimulate undifferentiated cells to become responsive to IGF-I.

The mechanism of action of GH-IGF-I axis on the kidney and other osmoregulatary organs in fishes has yet to be investigated. In mammals, IGF-I may mediate some (or all) of the renal actions of GH (Bern *et al.* 1991). IGF-I and IGF-I receptor mRNAs are both localized in the medullary thick ascending limbs in the kidney where IGF-I expression is GH-dependent (Chin *et al.* 1992). If this is true also in the salmonid kidney, IGF-I might affect, in an autocrine or paracrine manner, water reabsorption directly or indirectly through cell
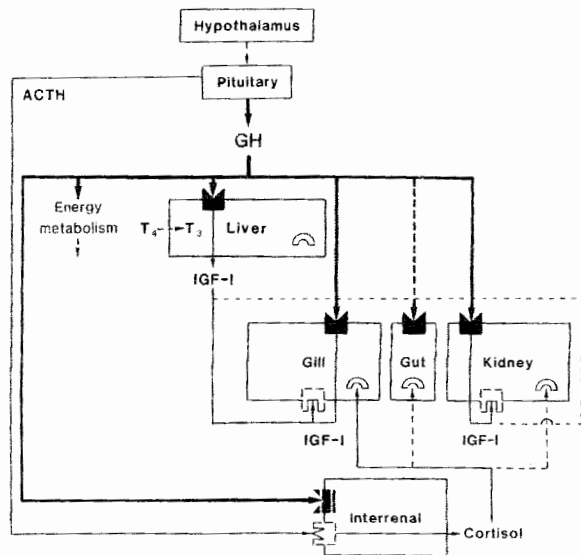
Fig. 1. Summary representation of GH action during seawater acclimation of salmonid fish. Continuous lines (arrows) denote confirmed pathways and broken lines possible pathways. Cortisol receptors are present in the gill, liver, intestine, kidney and muscle of brook trout and Atlantic salmon (Chakraborti *et al.* 1987; Chakraborti and Weisbart 1987; Weisbart *et al.* 1989). IGF-I receptors have yet to be identified. Response in the gill is reflected in stimulation of Na^+,K^+-ATPase activity and chloride cell differentiation.

proliferation and differentiation. Blazer-Yost and Cox (1989) found that IGF-I stimulates Na flux in toad urinary bladder. Local expression of IGF-I in gill chloride cells and accessory cells may also be possible. Further studies on the cell types of osmoregulatory organs that synthesize IGF-I and possess IGF-I receptors during acclimation to seawater are crucial to an understanding of the role of IGF-I.

Conclusions: A model for osmoregulatory actions of growth hormone

A model that explains the actions of GH during acclimation to seawater in salmonids is proposed (Fig. 1). The pituitary GH secretion and plasma GH concentrations increase after exposure to seawater; however, the control mechanisms at the pituitary/hypothalamus are unknown. Metabolic clearance rate of GH increases, and the increase may reflect increased GH binding to receptors. The magnitude

and duration of changes in the GH kinetics seem to be related to developmental stage and species. GH receptors are present in the liver, gill, intestine and kidney, although direct effects of GH have not yet been demonstrated by *in vitro* experiments. GH may influence acclimation to seawater through effects on other hormonal mediators. GH-IGF-I axis is operative in salmonids osmoregulation. Exogenous GH causes production of IGF-I in the liver, gill and kidney. IGF-I seems to be involved in acclimation to seawater at least through stimulation of gill Na^+,K^+-ATPase. The fact that exposure to seawater increases IGF-I mRNA in the gill and kidney suggests the importance of local expression of IGF-I in osmoregulatory organs. Clarification of the cell types that synthesize IGF-I in the osmoregulatory organs during acclimation to seawater will facilitate our understanding of the mechanisms of IGF-I action. GH is also known to sensitize the interrenal to ACTH, and cortisol can exert direct effects on the gill and possibly other osmoregulatory organs. GH may also act through thyroid hormones. Further research is needed to clarify the interaction between GH, cortisol, thyroid hormones, and IGF-I at several levels, especially secretion, circulating levels, kinetics, and the target organ.

Studies on the effect of GH on osmoregulatory physiology of other non-mammalian vertebrates are limited. Helms *et al.* (1987) observed increased GH secretion *in vitro* in response to increased osmotic pressure in tilapia weighing *ca.* 60 g. However, GH may not play an osmoregulatory role in the eel (see Olivereau and Ball 1970; Nagahama 1973; Hall and Chadwick 1978; Baker and Ingleton 1975; Suzuki *et al.* 1990, 1991; Duan and Hirano 1991). The eel can survive after hypophysectomy in either fresh water or seawater, whereas hypophysectomized salmonids are unable to survive in seawater but able to survive in fresh water (Nishioka *et al.* 1987).

The earlier demonstration that PRL is necessary to maintain plasma Na in certain euryhaline teleosts in fresh water and the subsequent identification of PRL-sensitive epithelia involved in ion transport focused attention on PRL-induced changes in electrolyte metabolism throughout the vertebrates (see

Brown and Brown 1987). We hope that the study on the role of GH in salmonid electrolyte metabolism has important implications for vertebrate endocrinology and general physiology.

Acknowledgements

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