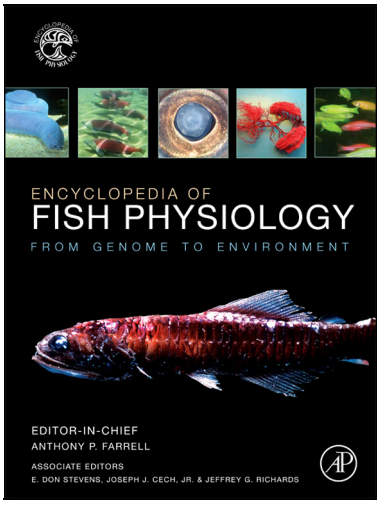

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HORMONAL CONTROLS

Hormonal Control of Metabolism and Ionic Regulation

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The Hormonal Control of Osmoregulation in Teleost Fish

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Glossary

Adrenocorticotrophic hormone (ACTH) A protein hormone produced in the pituitary that causes release of cortisol from the interregnal.
Anadromy Life-history strategy entailing reproduction and early rearing in freshwater followed by a significant growth phase in seawater.
Apoptosis The process of programmed cell death.
Cortisol The major corticosteroid of teleosts, produced in the interrenal and acting on metabolism and ion regulation.
Cystic fibrosis transmembrane conductance regulator (CFTR) An apical chloride channel involved in chloride secretion.
Euryhaline Animals that physiologically adjust to a wide range of water salinity are considered euryhaline (eury 'broad'; haline 'salt'), in contrast to stenohaline animals.
Growth hormone (GH) A pituitary protein hormone controlling growth, metabolism, and ion regulation.
Hormone Signaling molecule released by a cell that either stimulates the cell of origin (autocrine), nearby cells (paracrine), or travels via the bloodstream to distant cells (endocrine).
Insulin-like growth factor-I (IGF-I) A protein hormone produced in the liver in response to growth hormone and acting on growth and ion regulation.
Na^+,K^+-ATPase (NKA, the sodium pump) A major ATP-consuming ion pump that, directly or indirectly, drives many ion-regulatory processes, including maintaining sodium and ion gradients across cell plasma membranes and being present at high levels in ionocytes.
Na^+,K^+,$2Cl^-$ cotransporter (NKCC) An ion-translocating enzyme that utilizes a sodium gradient to transport Na^+, K^+, and Cl^- into the cell.
Prolactin A protein hormone produced in the pituitary acting on ion balance and reproduction.
Receptor A signal transduction molecule that is activated by a hormone.
Stenohaline Describes an organism that cannot live in environments that undergo large changes in salinity (steno 'narrow').
Thyroid hormones Thyroxine and triiodothyronine, produced in the thyroid gland and acting on development and metabolism.
Transactivation Binding of a transcription factor, such as a receptor–ligand complex, to DNA resulting in increased gene transcription.

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Introduction: Salt and Water Balance in Fish

Whether in freshwater or seawater, teleost fish maintain their plasma osmotic concentration at about one-third that of seawater (**see also Osmotic, Ionic and Nitrogenous-Waste Balance**: Osmoregulation in Fishes: An Introduction). In freshwater, this requires counteracting the passive gain of water and loss of ions, and is accomplished through the production of large volumes of dilute urine and active uptake of ions across the gills. In seawater, teleosts must counteract the passive gain of ions and loss of water. This is accomplished by drinking seawater, absorbing water and salts across the gut, and excreting monovalent ions across the gills and divalent ions through the kidney. It has been estimated that 95% of teleost species are stenohaline, living wholly in either freshwater or seawater. The remaining 5% are euryhaline, having the capacity to tolerate a wide range of salinities. This trait is widespread among teleost lineages and has apparently evolved many times, and may be one reason that teleosts can be found in almost all aquatic habitats.

As outlined above, the gills are the primary site of sodium and chloride transport, actively taking up salts in freshwater and excreting them in seawater. Most of the recent work on the endocrine control of ion transport in fish has focused on the gill, so this review will necessarily be biased in this direction. It has been known for some time that the mitochondrion-rich cell (also known as the chloride cell) is the site of salt secretion (**see also Role of the Gills**: Morphology of Branchial Ionocytes and **Osmotic, Ionic and Nitrogenous-Waste Balance**: Mechanisms of Gill Salt Secretion in Marine Teleosts). There is substantial evidence indicating that the major transporters involved in salt secretion in the gill include basolaterally located Na^+,K^+-ATPase (NKA, the sodium pump) and $Na^+,K^+,2Cl^-$ cotransporter (NKCC), and an apical Cl^- channel that is homologous with the cystic fibrosis transmembrane conductance regulator (CFTR) (**Figure 1**).

The site and mechanisms involved in ion uptake by the gill in freshwater are less certain. Both mitochondrion - rich cells and pavement cells may be involved in sodium and chloride uptake (**see also Osmotic, Ionic and**

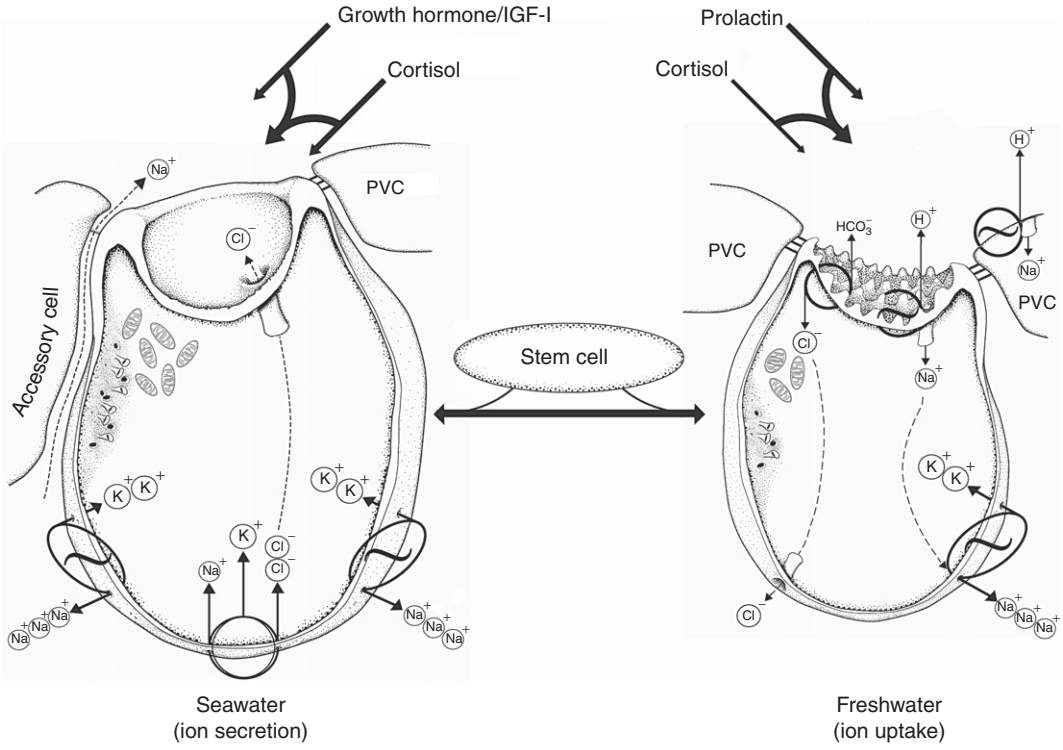

Figure 1 Morphology, transport mechanisms, and hormonal control of gill chloride cells in freshwater and seawater. Chloride cells are characterized by numerous mitochondria and an extensive tubular system that is continuous with the basolateral membrane. In seawater, mitochondrion-rich cells are generally larger and contain a deep apical crypt, whereas in freshwater, there is a broad apical surface containing numerous microvilli. Growth hormone and cortisol can individually promote the differentiation of the seawater chloride cell, and also interact positively to control epithelial transport capacity. Prolactin inhibits the formation of seawater chloride cells and promotes the development of freshwater chloride cells. Cortisol also promotes acclimation to freshwater by maintaining ion transporters and chloride cells, and by interacting to some degree with prolactin PVC, pavement cell. Reproduced from McCormick SD (2001) Endocrine control of osmoregulation in teleost fish. *American Zoologist* 41: 781–794.

Nitrogenous-Waste Balance: Mechanisms of Ion Transport in Freshwater Fishes). Chloride is exchanged for HCO_3^- at the apical surface and leaves at the basolateral membrane moving downhill on an electrical gradient (the chloride cell being more negative than the blood). Sodium may enter the gill epithelia by exchange with H^+, or through an apical Na^+ channel coupled to an apical H^+-ATPase, and pass into the bloodstream at the basolateral gill surface through NKA. Recent work suggests that in some species there is also a Na^+/Cl^- co-transporter on the apical surface that is involved in ion uptake. More direct evidence is needed to be certain of the roles and location of these transporters involved in ion uptake in teleosts.

There are three primary lines of evidence for the involvement of hormones in ion regulation. The first involves the treatment of animals (*in vivo*) or isolated tissues (*in vitro*) with hormones and examining ion regulatory performance and/or the response of ion transport proteins and cells. The second line of evidence comes from changes in circulating hormones when environmental salinity is changed, such as a transfer from freshwater to seawater. Third, the presence and regulation of specific hormone receptors in the organs and cell types responsible for ion regulation is taken as evidence for the involvement of that hormone in salt and water balance.

This article illustrates that there are many common features to the endocrine control of osmoregulation in teleost fish. It should be noted, however, that only a small number of teleosts have been examined and that we know little or nothing about the hormonal control of osmoregulation in the vast majority of fish. Given the great diversity among teleosts and the differing acclimation responses and strategies that have evolved, it should not be surprising to find that not all teleost fishes conform to a single scheme. Indeed, one of our outstanding research challenges is to determine how the hormonal control of osmoregulation differs among teleosts, and to what extent it has been shaped by natural selection.

Cortisol

Cortisol and Seawater Acclimation

Cortisol is the major corticosteroid produced by the interrenal tissue of teleost fish (**see also Hormonal Control of Metabolism and Ionic Regulation**: Corticosteroids). This hormone has several established physiological roles in osmoregulation, intermediary metabolism, growth, stress, and immune function. It has been shown for many species of euryhaline fish that treatment with cortisol in freshwater improves their subsequent survival and capacity to maintain low levels of plasma ions after exposure to seawater. This effect is due to increases in the size and abundance of gill mitochondrion-rich cells, which has been demonstrated *in vivo* and *in vitro*. Cortisol has also been shown to increase the transcription and abundance of the major transport proteins involved in salt secretion by the gill: NKA, NKCC, and CFTR. The effect of exogenous cortisol generally requires several days to reach its peak, suggesting that cell proliferation and differentiation are required for its complete action. In the intestine, exogenous cortisol stimulates NKA activity, together with ion and water absorption, thus improving acclimation to high environmental salinity. An increased drinking response after transfer to seawater has been observed in salmonids treated with cortisol.

Changes in circulating cortisol in response to increased environmental salinity are reported for many teleost species. The clearance rate (the inverse of the amount of time a compound remains in circulation) of cortisol also increases in seawater, suggesting increased utilization by osmoregulatory target tissues (**see also Integrated Control and Response of the Circulatory System**: Hormone Metabolism in the Circulation). The release of cortisol from the interrenal is primarily controlled by the pituitary hormone adrenocorticotrophic hormone (ACTH), though other endocrine factors may also be involved (**see also Hormonal Responses to Stress**: Hormone Response to Stress). Although there is evidence for activation of pituitary ACTH cells, salinity effects on circulating levels of ACTH have not been detected. ACTH production by the isolated pituitary does not appear to be directly responsive to changes in external osmolality. The increase in cortisol during osmotic stress occurs in both stenohaline and euryhaline fishes and may be part of a general stress response. Thus, the presence and regulation of cortisol receptors is also a critical component of osmoregulation in these fishes.

The classical signaling action of steroids begins by transport into the cell, followed by binding to a cytosolic receptor, which is then translocated into the nucleus. There, the steroid binds to specific genes to increase or decrease their expression. A large number of binding studies in fish have found evidence for a single class of corticosteroid receptors (CRs). These receptors are present in high concentrations in the gill, gut, and kidney, and their abundance is often altered by environmental salinity. During exposure to increased salinity, intracellular cortisol and CR levels in the gill shift from the cytosol to the nucleus, indicative of CR binding and translocation. High concentrations of CR have been found in the gill mitochondrion-rich cells.

In the past several years, molecular techniques have demonstrated the presence of genes in several teleost species related to the mammalian glucocorticoid receptors (GRs) and mineralocorticoid receptors (MRs). Two isoforms of fish GR genes have been found in several teleost species, and these have different activation affinities for cortisol. In addition, an MR-like gene has been

characterized in rainbow trout (*Oncorhynchus mykiss*) and the cichlid (*Haplochromis burtoni*). When the rainbow trout MR gene is expressed in a mammalian cell line, it was found to have high transactivation efficiency for both aldosterone and 11-deoxycorticosterone (DOC), similar to the binding characteristics of the mammalian MR. It has been suggested that DOC, present in the plasma of some teleosts at levels that could activate the fish MR, might be a mineralocorticoid in fish. Injection studies indicate, however, that DOC cannot carry out the seawater-adapting functions of cortisol. Thus, the physiological function of DOC and MR in fish remains to be established.

Cortisol and Freshwater Acclimation

As noted above, cortisol has largely been identified as a seawater-adapting hormone in a large number of teleost species. There is an increasing body of evidence demonstrating that cortisol is also involved in ion uptake, thus giving it a dual osmoregulatory function. Cortisol treatment in freshwater fish increases the surface area of gill mitochondrion-rich cells and the influx of sodium and chloride, affecting both renal and branchial functions. Survival and plasma ion levels of freshwater fish that have had their pituitary removed are increased by treatment with adrenocoritcotrophic hormone (ACTH), which can be presumed to be acting through its stimulation of cortisol release from the interrenal. Cortisol is also required to maintain water movement across the gut of freshwater eels. Cortisol treatment significantly increases the ion regulatory capacity of marine fish during exposure to low salinity and the ability of acid-resistant fish to maintain plasma sodium levels after exposure to acidic water.

Changes in circulating levels of cortisol also provide supporting evidence for a role of this hormone in ion uptake. Transfer of euryhaline species from seawater to freshwater results in short-term increases in plasma cortisol. Transfer of several species of marine fish from high to low salinity results in increased circulating cortisol that remains elevated for days to weeks. In Mozambique tilapia (*Oreochromis mossambicus*), transfer from freshwater to distilled water or injection of prolactin (PRL) results in elevated plasma cortisol. These studies on increasing cortisol levels in response to decreases in salinity, along with the cortisol treatment studies described above, provide evidence that, in many teleosts, cortisol has a physiological role in promoting ion uptake. This function of cortisol has not been fully appreciated due to an emphasis on the role of cortisol in salt secretion.

Although there is substantial evidence indicating that cortisol can increase gill and gut NKA, it is unclear whether this is primarily related to cortisol's seawater-adaptive effects, or whether upregulation of the sodium pump is also involved in ion uptake. If maintenance of the sodium pump is indeed integral to ion uptake, then the effect of cortisol on gill NKA could be one mechanism by which cortisol exerts a dual osmoregulatory function. In addition, cortisol also likely promotes the development of the freshwater morphology of chloride cells. Recent evidence indicates that in salmonids there are two salinity-dependent isoforms of gill NKA: one that is more abundant in freshwater and the other more abundant in seawater. Cortisol upregulates both of these isoforms, which is further evidence for a dual osmoregulatory role for this hormone.

Prolactin

By removing the pituitary (hypophysectomy) and then replacing the lost PRL with injections, Grace Pickford conclusively demonstrated 50 years ago that the pituitary hormone PRL was critical for the maintenance of ion balance of teleost fish in freshwater. Since then, evidence for PRL as an important freshwater-adapting hormone in fish comes from studies on exogenous PRL treatment, changes in PRL gene expression and circulating levels in response to salinity change, and the localization and regulation of PRL receptors.

Although PRL has been shown to have sodium- and chloride-retaining activity in a variety of freshwater and euryhaline teleosts, there is surprisingly little information on the cellular and biochemical effectors of the osmoregulatory actions of PRL. Throughout vertebrates, a large proportion of the various actions of PRL seem to be associated directly or indirectly with cell proliferation and/or apoptosis. PRL has been shown to affect chloride cells, both by inhibiting the development of seawater chloride cells and promoting the morphology of ion uptake cells. PRL treatment also reduces ion and water permeability of the esophagus and intestine, a response that normally occurs during acclimation to freshwater. PRL can induce intestinal cell proliferation in some euryhaline fishes. It has recently been shown that the abundance of NaCl co-transporter present on the apical surface of ion uptake cells in the tilapia gill decreases following hypophysectomy and is restored to original abundance with PRL treatment.

Gene expression, synthesis, secretion, and plasma levels of PRL all increase following exposure to freshwater. Metabolic clearance rate of PRL increases following fresh water acclimation of salmonids. In some teleosts such as tilapia, plasma osmolality and cortisol exert direct regulatory actions on PRL secretion. As in mammals, however, a specific hypothalamic PRL-releasing factor, PRL-releasing peptide (PrRP), has recently been identified in teleosts. PrRP promotes PRL transcription and secretion, with the histochemical localization of PrRP neuronal terminals near PRL cells in the pituitary. Moreover, PrRP seems to be an

essential stimulator of PRL since antiserum to PrRP decreases circulating PRL levels. In the amphibious euryhaline mudskipper (*Periophthalmus modestus*), the brain-pituitary axis of PrRP-PRL operates during both terrestrial and freshwater acclimation.

PRL receptor transcription and abundance are high in osmoregulatory organs such as the gill, intestine, and kidney. In the gill, the transcription and abundance of PRL receptor are lower in seawater than in freshwater in tilapia and salmonids. High levels of PRL receptor transcription have been found in mitochondrion-rich cells of the gill and enterocytes of the intestine.

There is evidence that both PRL and cortisol are necessary for normal ion regulation in freshwater. The two may even interact to control ion uptake. In hypophysectomized catfish (*Heteropneustes fossilis*), PRL and cortisol together cause a greater elevation of plasma ions than either hormone alone. Also, cortisol and PRL together have a greater effect than either hormone alone in promoting the transepithelial resistance and potential of an *in vitro* gill-cell preparation. In hypophysectomized and/or interrenalectomized fish, both PRL and/or ACTH or cortisol are necessary to completely restore ion and water balance in freshwater. Although an interaction between PRL and cortisol in controlling freshwater acclimation has been proposed, there is as yet little direct evidence for this hypothesis and no mechanism has been proposed.

Growth Hormone and IGF-I

In the 1950s, D.C.W. Smith observed that multiple injections of growth hormone could increase the capacity of brown trout to tolerate exposure to seawater. At first, this was attributed to the growth effect of the hormone because size confers greater salinity tolerance in salmonids. Several decades later, it was found that a single injection of growth hormone in unfed fish was sufficient to increase salinity tolerance, indicating a relatively rapid effect that was independent of body size. Growth hormone has since been shown to increase the number and size of gill mitochondrion-rich cells as well as the abundance of NKA and NKCC (**see also Cellular, Molecular, Genomics, and Biomedical Approaches**: Growth Hormone Overexpression in Transgenic Fish).

A major route of the osmoregulatory action of GH is through its capacity to increase circulating levels and local tissue production of insulin-like growth factor-I (IGF-I). Exogenous treatment of IGF-I has been found to increase the salinity tolerance of rainbow trout, Atlantic salmon (*Salmo salar*), and killifish (*Fundulus heteroclitus*). GH cannot directly (in culture) increase gill NKA activity, whereas IGF-I can. The ability of prior GH treatment to increase *in vitro* responsiveness of gill tissue to IGF-I further suggests an indirect action of GH on gill tissue, and a direct action of IGF-I. Levels of IGF-I mRNA in gill and kidney increase following GH injection and exposure to seawater, indicating that local production of IGF-I may act in a paracrine fashion to influence transport capacity of gill and renal epithelia.

In addition to the effects of exogenous hormones, changes in gene expression, secretion, circulating levels, and metabolic clearance rate of growth hormone and IGF-I also provide evidence for the osmoregulatory actions of the GH/IGF-I axis in several euryhaline species. Plasma GH levels have also been found to increase in stenohaline freshwater fish following exposure to brackish water (e.g., 12 ppt). Following exposure of rainbow trout to seawater, there are increases in plasma levels of IGF-I and three of its binding proteins. IGF-I mRNA levels in liver, gill, and kidney increase following growth hormone injection and exposure to seawater, indicating that local production of IGF-I may also act to influence transport capacity of gill and renal epithelia. IGF-I has been found specifically in gill chloride cells whose number and/or size are stimulated by growth hormone.

Growth hormone receptors in high concentrations have been found in the liver, gill, gut, and kidney of euryhaline teleost fish. Occupancy of hepatic growth hormone receptors by growth hormone increased following exposure to seawater. Growth hormone transcription has also been detected in osmoregulatory organs and may be acting in an autocrine or paracrine manner in these tissues. Growth hormone receptor mRNA levels in the gill increase after seawater acclimation of salmonids. Specific high-affinity, low-capacity IGF-I receptors have been found in gill tissue of salmon and tilapia, and have been immunocytochemically localized to gill chloride cells in striped bass (*Morone saxatilis*) and tilapia.

Few teleost species have been examined for the physiological impact of the GH/IGF-I axis on osmoregulation. Exogenous treatments have been found to affect salmonids, tilapia, and killifish. Changes in circulating hormones and production of IGF-I in osmo-regulatory organs in salmonids provide convincing evidence for both endocrine and paracrine actions of the GH/IGF-I axis, but there is relatively little information in this area from other teleosts. There is no apparent osmoregulatory role for GH in sea bream, a marine species with a limited capacity for hyperosmoregulation. Species variation linked to different ion regulatory capacities and/or strategies for ion regulation may determine to what extent the GH/IGF-I axis is involved in osmoregulation. A similar situation may occur for PRL: there may be limited osmoregulatory effects of PRL in stenohaline marine teleosts where any ion uptake may be maladaptive. Expanded research on both euryhaline and stenohaline species will be necessary to determine how widespread the osmoregulatory actions of PRL and the GH/IGF-I axis are among

teleosts, and how phyletic histories and natural selection have acted to bring about any observed patterns.

Interaction of the GH/IGF-I Axis with Cortisol

The GH/IGF-I and cortisol axes work together to regulate salt secretion in teleosts. Injection of GH and cortisol together increases gill NKA activity and salinity tolerance in salmonids and killifish to a greater extent than either hormone alone. This effect can be seen in both hypophysectomized and intact fish. Cortisol treatment of freshwater Atlantic salmon causes an increase in both the freshwater and seawater isoforms of NKA, but treatment with GH and cortisol causes the seawater isoform to increase to an even greater extent, and the freshwater isoform to decrease. Much of the interaction of GH and cortisol is through GH's capacity to upregulate the number of gill cortisol receptors, which makes the tissue more responsive to cortisol.

Growth hormone increases mitotic activity in several cell types in the gill of rainbow trout. Cortisol has no effect on mitotic activity but increases the number of chloride cells, suggesting that cortisol acts primarily to promote differentiation of chloride cells. Therefore, another pathway for GH/IGF-I and cortisol interaction is stimulation of stem cell proliferation by GH and/or IGF-I, creating more stem cells that can then be acted on by cortisol. The GH/IGF-I axis and cortisol may also interact at higher regulatory pathways, such as the hypothalamus and pituitary. *In vivo* and *in vitro* exposure to GH increases the sensitivity of interrenal tissue to ACTH, causing increased release of cortisol. Corticotropin-releasing hormone is a potent stimulator of *in vitro* growth hormone release in the European eel (*Anguilla anguilla*).

Thyroid Hormones

Although there is conflicting evidence regarding the role of thyroid hormones in osmoregulation, most studies have found that thyroid hormones, by themselves, cannot increase ion uptake or secretory capacity. Exceptions to this are prolonged thyroxine (T4) treatment that accelerated smolt-related increases in gill mitochondrion-rich cells and NKA activity in Atlantic salmon, and dietary triiodothyronine (T3) treatment that increased the number of gill mitochondrion-rich cells without affecting gill NKA activity. Thyroid hormones play at least a supportive role in seawater acclimation, and may interact with both the GH/IGF-I and cortisol axes. Inhibition of the thyroid axis with thioruea in killifish caused increased plasma ions in seawater but had no effect in freshwater. T4 treatment alone has no effect, but potentiates the action of cortisol on gill NKA activity in tilapia, and the action of GH on gill NKA activity in salmon. Inhibiting the conversion of T4 to T3 interferes with normal and GH-induced seawater acclimation in trout. T3 treatment increases the number of gill cortisol receptors in trout and salmon. Thyroid hormones thus appear to exert their influence on salt secretory mechanisms primarily through an interaction with cortisol and the GH/IGF-I axis.

The Special Case of Anadromy

As part of their normal life history, anadromous fish (such as salmon) must move between freshwater and seawater at least twice during their life history (**see also Fish Migrations**: Pacific Salmon Migration: Completing the Cycle). As juveniles in freshwater, salmon have only a limited capacity to enter seawater. At the time of their downstream migration (when they are known as smolts), juvenile salmon develop a very high capacity for salt secretion before they actually arrive in the ocean. The timing of this developmental process differs among salmonids, but is accompanied by changes in the gill (increased mitochondrion-rich cells, NKA, and NKCC), gut, and kidney.

During smolt development, GH, IGF-I, and cortisol increase in response to developmental and/or environmental cues such as photoperiod and temperature (**Figure 2**). PRL can inhibit smolt development, and increases early during smolt development, but then decreases at the peak of smolting. Thyroid hormones also increase during smolting and are thought to play an indirect role in osmoregulatory changes, but a direct role in morphological, metabolic, and behavioral changes. Thus, the same hormones that are altered by exposure to salinity in other species increase prior to seawater exposure in salmon, inducing preparatory changes in salt secretory mechanisms that allow rapid movement into seawater with minimal osmotic perturbations.

The developmental changes that occur during smolting in salmon appear to be similar to other species, such as lamprey and shad that make just one or a few migrations from freshwater to seawater. Species that make more frequent migrations between freshwater and seawater may rely more on rapid regulation ion uptake or salt secretion rather than developmentally cued regulation.

Summary

Cortisol has long been known to have an important role in seawater acclimation of teleost fishes. Current evidence indicates that the GH/IGF-I axis also has a role in seawater acclimation, and that GH, IGF-I, and cortisol interact positively to promote salt secretion and the underlying physiological mechanisms. PRL has a

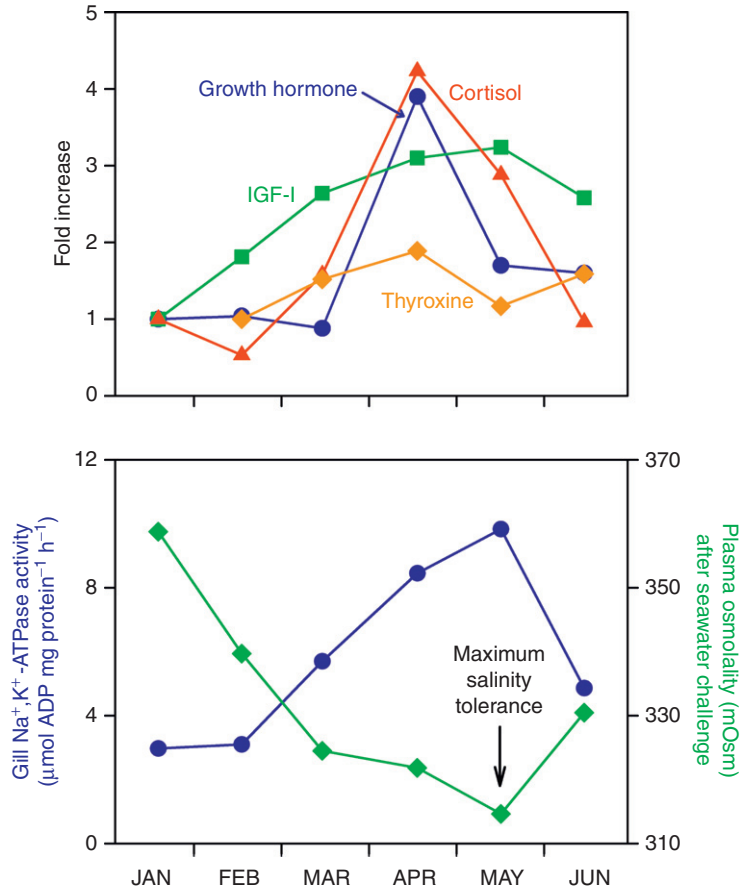

Figure 2 Changes in plasma hormone levels, gill NKA activity, and salinity tolerance during the parr–smolt transformation of Atlantic salmon. Interaction among cortisol, growth hormone, IGF-I, and thyroid hormones results in physiological changes that are preparatory for seawater entry. Adapted from McCormick SD, Lerner DT, Monette MY, Nieves–Puigdoller K, and Björnsson BTh (2009) Taking it with you when you go: How perturbations to the freshwater environment, including temperature, dams and contaminants, affects seawater performance of anadromous fish. In: Haro AJ, Smith KL, Rulifson RA, *et al.* (eds.) *Challenges For Diadromous Fishes in a Dynamic Global Environment.* American Fisheries Society Symposium, vol. 69, pp. 195–214. Bethesda, MD, USA.

well-established role in ion uptake and inhibition of salt secretion. In addition to its role in seawater acclimation, several studies indicate that cortisol is also involved in ion uptake and can interact positively with PRL, indicating that cortisol has a dual osmoregulatory function in teleosts. The action of cortisol in promoting ion uptake or secretion may therefore depend partly on its interaction with growth hormone and PRL: when growth hormone is high and PRL is low, cortisol may act primarily to promote salt secretion. Conversely, when growth hormone is low and PRL is elevated, cortisol will act to promote ion uptake.

See also: **Cellular, Molecular, Genomics, and Biomedical Approaches**: Growth Hormone Overexpression in Transgenic Fish. **Fish Migrations**: Pacific Salmon Migration: Completing the Cycle. **Hormonal Control of Metabolism and Ionic Regulation**: Corticosteroids. **Hormonal Responses to Stress**: Hormone Response to Stress. **Integrated Control and Response of the Circulatory System**: Hormone Metabolism in the Circulation. **Osmotic, Ionic and Nitrogenous-Waste Balance**: Mechanisms of Gill Salt Secretion in Marine Teleosts; Mechanisms of Ion Transport in Freshwater Fishes; Osmoregulation in Fishes: An Introduction. **Role of the Gills**: Morphology of Branchial Ionocytes.

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