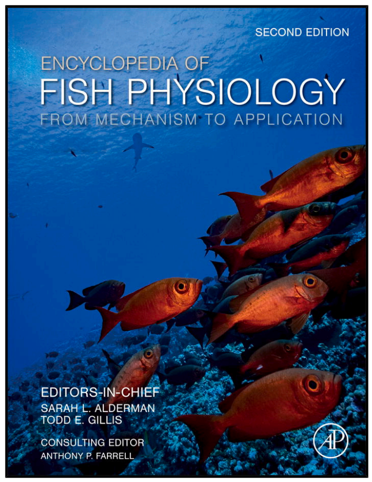

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The hormonal control of osmoregulation in fish

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This is an update of S.D. McCormick, HORMONAL CONTROL OF METABOLISM AND IONIC REGULATION | The Hormonal Control of Osmoregulation in Teleost Fish, Edited by Anthony P. Farrell, Encyclopedia of Fish Physiology, Academic Press, 2011, Pages 1466–1473, ISBN 9780080923239.

Key points

- Cortisol promotes both ion uptake and salt secretion and thus has an osmoregulatory role in freshwater and seawater.
- The growth hormone/insulin-like growth factor I axis promotes seawater acclimation and interacts with cortisol.
- Prolactin promotes freshwater acclimation and inhibits seawater acclimation and may interact with cortisol.

Glossary

Adrenocorticotropic hormone (ACTH) A protein hormone primarily produced in the pituitary that causes release of cortisol from the interrenal.
Amphihaline Capable of living in either freshwater or seawater.
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 Able to withstand a wide range of salinities.
Growth Hormone (GH) A pituitary protein hormone controlling growth, metabolism and ion regulation.
Hormone A molecule produced in an endocrine organ that is carried through the blood and acts as a chemical signal in another part of the body.
Insulin-like growth factor I (IGF-I) A protein hormone produced primarily in the liver in response to growth hormone and acting on growth and ion regulation.
Prolactin A protein hormone primarily produced in the pituitary acting on ion balance and reproduction.
Receptor A signal transduction molecule that is activated by a hormone.
Stenohaline Restricted to a narrow salinity range (i.e., freshwater or seawater).
Na^+/K^+-ATPase (NKA, the sodium pump) An energy-demanding transport protein located in the basolateral membrane that moves sodium out and potassium into the cell.
$Na^+/K^+/2Cl^-$ cotransporter (NKCC) An ion-translocating enzyme that utilizes a sodium gradient to transport Na^+, K^+ and Cl^- into the cell.
Thyroid hormones Thyroxine and triiodothyronine, produced in thyroid follicles 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.

Encyclopedia of Fish Physiology, Second Edition, 2024, 293–300

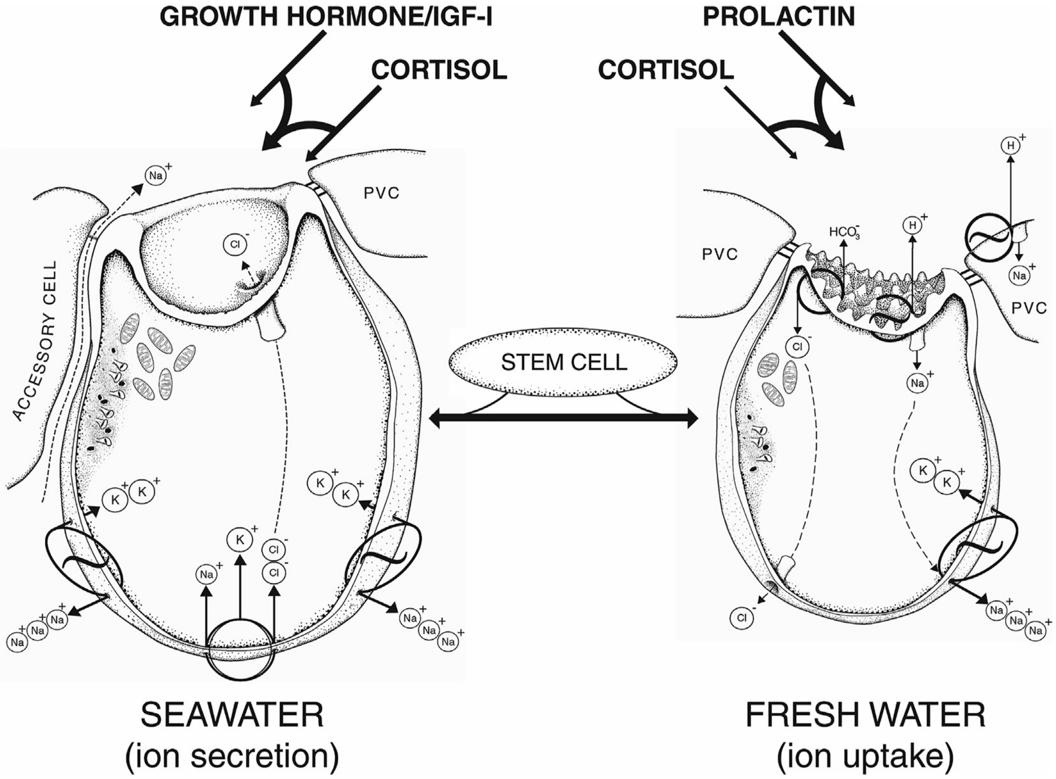
List of abbreviations

ACTH Adrenocorticotropic hormone
CFTR Cystic fibrosis transmembrane conductance regulator
CR Corticosteroid receptors
DOC 11-deoxycorticosterone
FW Freshwater
GH Growth hormone
GR Glucocorticoid receptor
IGF-I Insulin-like growth factor I
MR Mineralocorticoid receptor
NKA Na^+/K^+-ATPase (sodium, potassium adenosine triphosphatase)
NKCC $Na^+/K^+/2Cl^-$ cotransporter (sodium, potassium, 2 chloride cotransporter)
PrRP Prolactin-releasing peptide
SW Seawater

Abstract

Hormones control the physiological alterations necessary for ion homeostasis when fish move between freshwater and seawater. Cortisol promotes seawater acclimation through differentiation of salt-secreting ionocytes and ion transport proteins in the gill. The growth hormone/insulin-like growth factor I axis is also important in seawater acclimation and acts in synergy with cortisol. Prolactin is important in freshwater acclimation through regulation of ion and water permeability in the gill, gut, and kidney. Cortisol also promotes ion uptake, thus having a dual osmoregulatory action, and may interact with prolactin during freshwater acclimation. These generalizations are based on results from a small number of "model" species; since natural selection for different habitats and life histories has shaped the hormonal control of osmoregulation, differences among species should be expected.

Teaching slide



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Introduction: Salt and water balance in fish

Whether in freshwater (FW) or seawater (SW), teleost fish maintain their plasma osmotic concentration at about one-third that of SW. In FW 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 SW, teleosts must counteract the passive gain of ions and loss of water which is accomplished by drinking SW, absorbing water and salts across the gut, and excreting monovalent ions across the gills and divalent ions through the kidney (Evans et al., 2005; Edwards and Marshall, 2013). It has been estimated that 95% of teleost species are stenohaline, living wholly in either FW or SW. The remaining 5% are amphihaline having the capacity to live in either of these habitats. This trait is present in a number of teleost lineages and thus appears to have evolved many times and may be one reason that teleosts can be found in almost all aquatic habitats (Schultz and McCormick, 2013; Betancur-R et al., 2015).

As outlined above, the gills are the primary site of sodium and chloride transport, actively taking up salts in FW and excreting them in SW. Most of the recent work on the endocrine control of ion transport in fish has focused on the gill, so this article will necessarily be biased in this direction. It has been known for some time that ionocytes (also known as mitochondrion-rich cells or chloride cells) are the site of salt secretion (Hiroi and McCormick, 2012). 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 $Na^+/K^+/2Cl^-$ co-transporter (NKCC), and an apical Cl^- channel that is homologous with the cystic fibrosis transmembrane conductance regulator (CFTR) (**Fig. 1**).

The site and mechanisms involved in ion uptake by the gill in FW are less certain and appear to vary among species (Hwang et al., 2011). Both ionocytes and pavement cells may be involved in sodium and chloride uptake. Chloride is exchanged for HCO_3^- at the apical surface and leaves at the basolateral membrane moving "downhill" on an electrical gradient (the ionocyte 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 then 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 (NCC) 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 with respect to 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 whole animals (*in vivo*) or isolated tissues or cells (*ex vivo*, *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 FW to SW. Third, the presence and regulation of specific hormone receptors in the organs and cell types responsible for ion regulation also provides evidence for the involvement of that hormone in salt and water balance. This article will focus on the more long-term activation of cells and transporters involved in whole animal osmoregulatory capacity; the role of rapid acting hormones in the control of fluid intake and fluid balance is covered elsewhere.

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 fishes. Most of the fish examined to date are amphihaline or euryhaline species, with relatively little known about stenohaline species. Given the great diversity among teleosts and the differing life histories, acclimation responses and strategies that have evolved, it should be unsurprising 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 and seawater acclimation

Cortisol is the major corticosteroid produced by the interrenal tissue of teleost fish (Mommsen et al., 1999; Schreck et al., 2016). This hormone has several established physiological roles in osmoregulation, intermediary metabolism, growth, stress, memory and immune function. It has been shown for many species of euryhaline fish that treatment with cortisol in FW improves their subsequent survival and capacity to maintain low levels of plasma ions after exposure to SW (McCormick, 2001; Takei and McCormick, 2013). This effect is due at least in part to cortisol's ability to increase the size and abundance of gill SW-type ionocytes, 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. Cortisol also increases some intercellular junction proteins (claudins and occludins) that are also upregulated following exposure to SW. The effect of exogenous cortisol generally requires several days to reach its peak, suggesting that cell differentiation is required for its complete action. Cortisol activation of foxi 3 appears to be necessary for ionocyte differentiation. 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 SW has been observed in salmonids treated with cortisol.

Changes in circulating cortisol in response to increased environmental salinity are reported for many teleosts. The clearance rate (the inverse of the amount of time a compound remains in circulation) of cortisol also increases in SW, suggesting increased utilization by osmoregulatory target tissues. The release of cortisol from the interrenal is primarily controlled by the pituitary hormone adrenocorticotropic hormone (ACTH), though other endocrine factors may also be involved. Exposure of rainbow trout (*Oncorhynchus mykiss*) to SW results in elevated transcription of corticotropin-releasing factor (CRF) in the hypothalamus followed by increases in plasma ACTH and cortisol levels. ACTH production by the isolated pituitary does not appear to be directly responsive

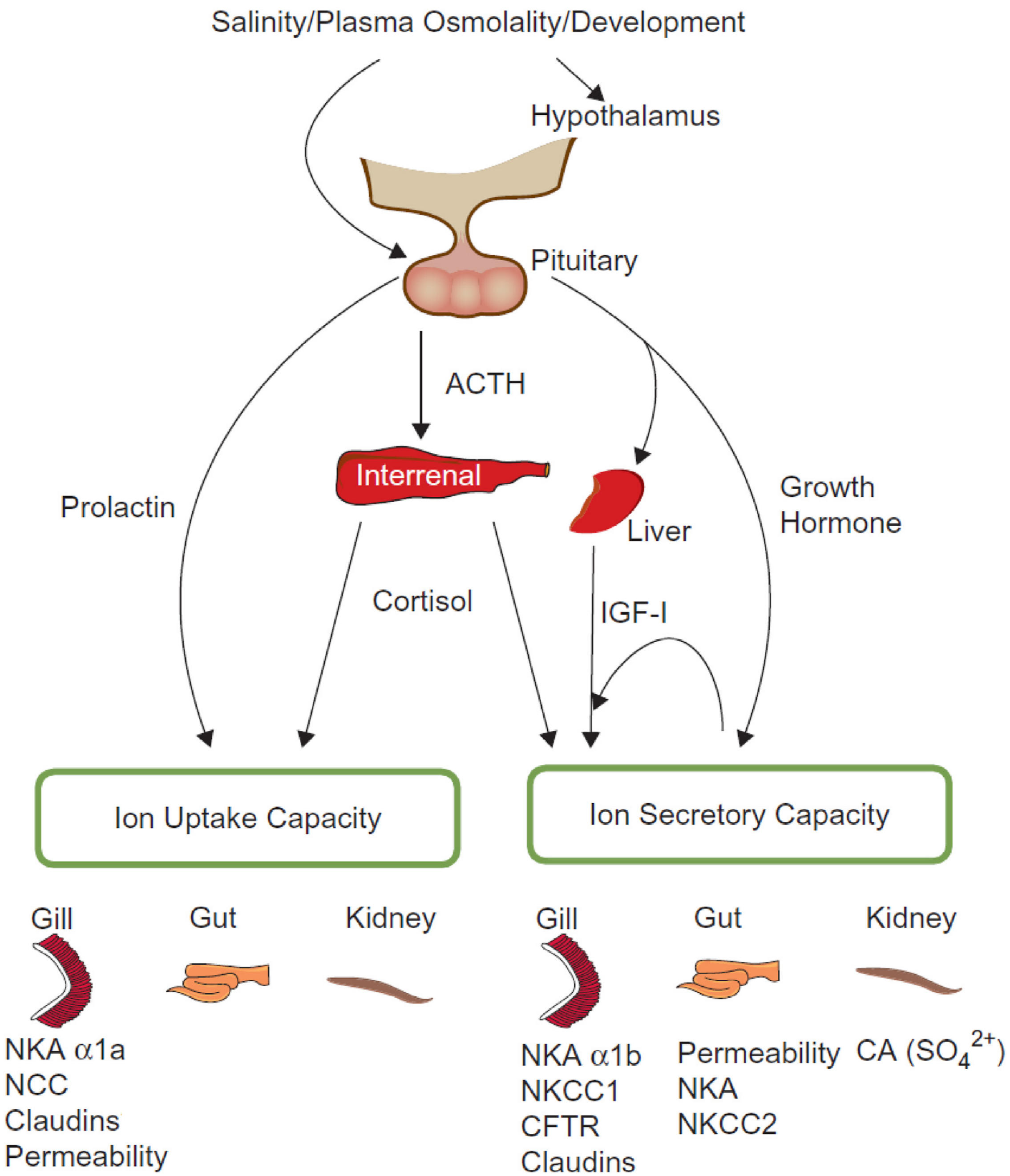

Fig. 1 Hormonal control ion uptake (freshwater) and salt secretory (seawater) capacity of euryhaline fish, emphasizing the effects of prolactin and cortisol in promoting ion uptake and the interaction of the GH/IGF-I axis and cortisol in promoting ion secretion. The lower part of the figure shows proteins involved in osmoregulation that are known to be under the control of these endocrine systems for gill, gut and kidney. Abbreviations: ACTH, adrenocorticotropic hormone; IGF-I, insulin-like growth factor I; NKA, Na^+/K^+-ATPase; NCC, Na^+/Cl^- cotransporter; NKCC, $Na^+/K^+/2Cl^-$ cotransporter; CFTR, cystic fibrosis transmembrane regulator; CA, carbonic anhydrase. Adapted from Takei, Y., and McCormick, S.D., 2013. Hormonal control of fish euryhalinity. In: McCormick, S.D., et al. (ed.), Fish Physiology Vol. 32 Euryhaline Fishes. Academic Press, Amsterdam.

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 fish.

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 where it binds to specific genes to increase or decrease their expression. Many binding studies in fish have found evidence for high-affinity, low-capacity corticosteroid receptors (CR) that 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 ionocytes. Molecular genetic approaches have demonstrated the presence of genes homologous with the mammalian glucocorticoid (GR) and mineralocorticoid receptors (MR) in teleosts. Two isoforms of GR have been found in most (but not all) teleost species, and these have different activation affinities for cortisol which may have physiological relevance for their response to environmental salinity. For instance, cortisol's action to induce differentiation of gill ionocytes in medaka (*Oryzias latipes*) is dependent on GR2 and not GR1. 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 MR, might be a mineralocorticoid in fish. Injection studies indicate, however, that DOC cannot carry out the SW-adapting functions, but that some of the actions of cortisol in osmoregulation (e.g., regulation of specific claudins) may work through MR. Thus, the physiological function of DOC and MR in fish remains to be established, and the use of "mineralocorticoid" and "glucocorticoid" to describe hormones and receptors in fish should be used with some caution, since clear distinctions in their major function may not exist.

Cortisol and freshwater acclimation

As noted above, cortisol has been identified as a SW-adapting hormone in many teleost species. There is increasing evidence that cortisol is also involved in ion uptake, thus giving it a dual osmoregulatory function (Takei and McCormick, 2013). Cortisol treatment in some FW teleosts increases the surface area of FW-type ionocytes in the gill and the influx of sodium and chloride. Survival and plasma ion levels of FW fish that have had their pituitary removed are increased by treatment with 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 FW Japanese eels (*Anguilla japonica*). 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 low pH 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 SW to FW 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 FW to distilled water or injection of prolactin 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 SW-adaptive effects, or whether upregulation of the sodium pump is also involved in ion uptake. Presence of the sodium pump in FW-type ionocytes is critical for ion uptake, so 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 "FW" morphology and function of gill ionocytes. In salmonids there are two salinity-dependent isoforms of gill NKA: one that is more abundant in FW and the other more abundant in SW. Cortisol upregulates both of these isoforms, which is further evidence for a dual osmoregulatory role for this hormone. The cotransport protein NCC, which is involved in ion uptake in many (but not all) FW teleosts, is upregulated by cortisol. Cortisol has also been shown to upregulate several specific claudins and occludins that are normally elevated in FW fish.

Prolactin

By removing the pituitary (i.e., hypophysectomy) and then replacing the "lost" prolactin (PRL) with injections, Grace Pickford conclusively demonstrated more than 60 years ago that this pituitary hormone was critical for mummichog (*Fundulus heteroclitus*) to maintain ion balance in FW. Similar results have been found for tilapia, but in salmonids hypophysectomy does not reduce survival or plasma ion levels in FW. Whole-animal knockout of PRL in zebrafish (*Danio rerio*) compromises survival in FW but not in brackish water. It should be noted that there is increased recognition that extra-pituitary production of PRL (and growth hormone) can have physiologically relevant effects.

Although PRL has been shown to have sodium- and chloride-retaining activity in a variety of FW and euryhaline teleosts (Manzon, 2002; Sakamoto and McCormick, 2006), the cellular and biochemical effectors of the osmoregulatory actions of PRL have only recently been examined (Breves et al., 2014). 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 gill ionocytes, both by inhibiting the development of SW-type ionocytes 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 FW acclimation. PRL can induce intestinal cell proliferation in some euryhaline fishes. Abundance of NCC present on the apical surface of FW-type gill ionocytes decreases following hypophysectomy and is restored to original abundance with prolactin treatment in tilapia. Some of the gill and intestinal claudins that increase following transfer of teleosts from SW to FW are upregulated by PRL.

Gene expression, synthesis, secretion and plasma levels of PRL all increase during FW acclimation of tilapia. Metabolic clearance rates of PRL in salmonids are also increased following FW acclimation. In some teleosts, plasma osmolality and cortisol exert direct regulatory actions on PRL secretion. A specific hypothalamic prolactin-releasing peptide (PrRP) has recently been identified in teleosts. PrRP promotes PRL transcription and secretion, with the histochemical localization of PrRP neuronal terminals near prolactin cells in the pituitary. Moreover, PrRP seems to be an essential stimulator of prolactin in some species since antiserum to PrRP decreases circulating prolactin levels. In the amphibious euryhaline mudskipper (*Periophthalmus modestus*), the brain-pituitary axis of PrRP-prolactin is activated during both terrestrial and FW acclimation.

Prolactin 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 SW than in FW in tilapia, salmonids and flounder. High levels of PRL receptor transcription have been found in gill ionocytes and intestinal enterocytes.

Prolactin generally inhibits mechanisms of ion secretion which is often the opposite of the cortisol stimulatory effect. But there is evidence that both PRL and cortisol are necessary for normal ion regulation in FW, and the two hormones may interact to control ion uptake. Cortisol promotes prolactin release in salmonids. In hypophysectomized catfish (*Heteropneustes fossilis*), prolactin and cortisol together cause a greater elevation of plasma ions than either hormone alone. Using *in vitro* approaches, cortisol and PRL together have a greater effect than either hormone alone in promoting the transepithelial resistance and transcription of NCC and the FW isoform of NKA. In hypophysectomized and/or interrenalectomized fish, both PRL and either ACTH or cortisol are necessary to completely restore ion and water balance in FW. However, there are several transporters involved in ion uptake that do not appear to be coregulated by PRL and cortisol, indicating selective pathways for their interaction.

Growth hormone and IGF-I

In the 1950's, D.C.W. Smith observed that multiple injections of growth hormone could increase the capacity of brown trout (*Salmo trutta*) to tolerate exposure to SW. 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 SW-type gill ionocytes as well as the abundance of NKA and NKCC (Takei and McCormick, 2013).

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) (Sakamoto and McCormick, 2006). Exogenous IGF-I treatment has been found to increase the salinity tolerance of rainbow trout, Atlantic salmon (*Salmo salar*) and killifish. GH cannot directly (*in vitro*) 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 SW, indicating that local production of IGF-I may act in a paracrine fashion to influence transport capacity of gill and renal epithelia.

Plasma GH levels have also been found to increase in stenohaline FW fish following exposure to brackish water (e.g., 12 parts per thousand). Plasma levels of IGF-I and three of its binding proteins increase following SW acclimation in rainbow trout. IGF-I mRNA levels in liver, gill and kidney increase following GH injection and exposure to SW, 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 ionocytes whose number and/or size are stimulated by GH.

High concentrations of GH receptors have been found in the liver, gill, gut and kidney of euryhaline teleost fish. Occupancy of hepatic receptors by GH increased following exposure to SW, which may relate to the liver's production of IGF-I. Growth hormone transcription also has 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 SW acclimation of salmonids. Specific high-affinity, low-capacity IGF-I receptors have been found in gill tissue of salmon and tilapia and have been localized to gill ionocytes 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 osmoregulatory 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 (*Sparus auratus*), 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 most ion uptake by the gill would be maladaptive. Expanded research on both euryhaline and stenohaline species will be necessary to determine how widespread the osmoregulatory actions of the GH/IGF-I axis is among teleosts, and what phylogenetic histories and evolutionary pressures have acted to bring about any observed patterns. Studies on euryhaline teleosts indicate that the GH/IGF-I axis, prolactin and their receptors have been differentially altered by natural selection in FW and SW habitats.

Interaction of the GH/IGF-I axis with cortisol

The GH/IGF-I and cortisol axes work together to regulate salt secretion in several euryhaline teleosts (Takei and McCormick, 2013). 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 synergistic effect can be seen in both hypophysectomized and intact fish. Cortisol treatment of FW Atlantic salmon causes an increase in both the FW and SW isoforms of NKA, but treatment with GH and cortisol causes the SW isoform to increase to an even greater extent, and the FW isoform to decrease. Much of the interaction of GH and cortisol is through GH's capacity to upregulate the number of gill CR, which makes the tissue more responsive to cortisol. GH also increases the sensitivity of the interrenal to ACTH resulting in greater cortisol production.

Growth hormone increases mitotic activity in several cell types in the gill of rainbow trout. Cortisol has no effect on gill mitotic activity but increases the number of gill ionocytes, suggesting that cortisol acts primarily to promote their differentiation. Thus, another pathway for GH/IGF-I and cortisol interaction appears to be 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 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 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 (T_4) treatment that accelerated smolt-related increases in gill ionocytes and NKA activity in Atlantic salmon, and dietary triiodothyronine (T_3) treatment that increased the number of gill ionocytes without affecting gill NKA activity. Thyroid hormones play at least a supportive role in SW acclimation and may interact with both the GH/IGF-I and cortisol axes. Inhibition of the thyroid axis with thiourea in killifish caused increased plasma ions in SW but had no effect in FW. T_4 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

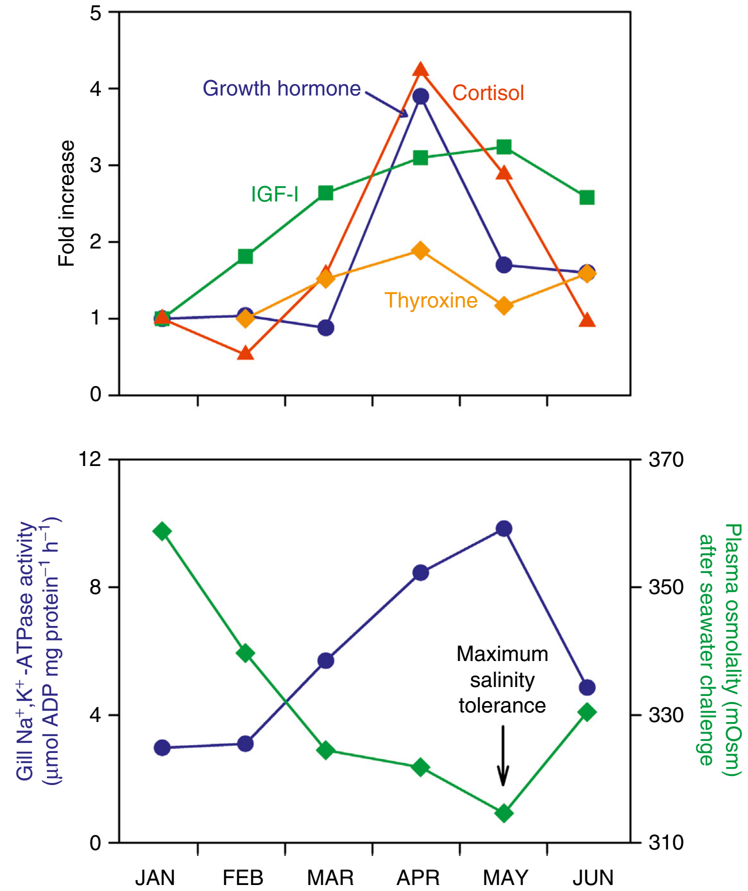

Fig. 2 Changes in plasma hormone levels, gill Na^+/K^+-ATPase activity and salinity tolerance during the parr-smolt transformation of Atlantic salmon. Interaction among cortisol, growth hormone, insulin-like growth factor I (IGF-I) and thyroid hormones result in physiological changes that are preparatory for seawater entry. Adapted from McCormick, S.D., Lerner, D.T., Monette, M.Y., Nieves-Puigdoller, K., Björnsson, B.Th., 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, A.J., Smith, K.L., Rulifson, R.A., Moffitt, C.M., Klauda, R.J., Dadswell, M.J., Cunjak, R.A., Cooper, J.E., Beal, K.L., Avery, T.S. (eds.), Challenges for Diadromous Fishes in a Dynamic Global Environment. American Fisheries Society Symposium 69, 195–214. Bethesda, Maryland, USA.

T_4–T_3 interferes with normal and GH-induced SW acclimation in trout. T_3 treatment increases the number of CR in the gills of 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 FW and SW at least twice during their life history. As juveniles in FW, salmon have only a limited capacity to enter SW. At the time of their downstream migration (when they are known as smolts), juvenile salmon develop a very high capacity for salt secretion even before they arrive at the ocean. The timing of this developmental process differs among salmonids but is accompanied by changes in the gill (increased branchial SW-type ionocytes and the SW isoforms of 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 (**Fig. 2**). PRL can inhibit smolt development and is elevated early in 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 necessary for SW transition. Thus, the same hormones that are altered by exposure to salinity in other species increase prior to SW exposure in salmon, inducing preparatory changes in salt secretory mechanisms that allow rapid movement into SW with minimal osmotic perturbations (McCormick, 2013).

The developmental changes that occur during smolting in salmon appear to be similar to other species, such as sea lamprey (*Petromyzon marinus*) and American shad (*Alosa sapidissima*) that make just one or a few migrations from FW to SW (McCormick, 2009). Species that make more frequent migrations between FW and SW may rely more on rapid regulation of ion uptake or salt secretion rather than developmentally cued regulation.

Summary/conclusion

Cortisol has long been known to have an important role in SW acclimation of teleost fishes. Current evidence indicates that the GH/IGF-I axis also has a role in SW acclimation, and that GH, IGF-I and cortisol work synergistically to promote salt secretion and the underlying physiological mechanisms. PRL has a well-established role in ion uptake and inhibition of salt secretion. In addition to its role in SW 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 in part on its interaction with GH and PRL: when GH is high and PRL low, cortisol may act primarily to promote salt secretion. Conversely, when GH is low and PRL elevated, cortisol will act to promote ion uptake.

See Also: Endocrine structures and organs; Hormonal control of fluid intake and fluid balance; Osmoregulation in chondrichthyan fishes; Osmoregulation in fishes: An introduction; Plasticity in gill morphology and function; The kidney for osmoregulation; The pituitary gland of fishes; Water balance and aquaporins.

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