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Prolactin and growth hormone in fish osmoregulation

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Abstract

Prolactin is an important regulator of multiple biological functions in vertebrates, and has been viewed as essential to ion uptake as well as reduction in ion and water permeability of osmoregulatory surfaces in freshwater and euryhaline fish. Prolactin-releasing peptide seems to stimulate prolactin expression in the pituitary and peripheral organs during freshwater adaptation. Growth hormone, a member of the same family of hormones as prolactin, promotes acclimation to seawater in several teleost fish, at least in part through the action of insulin-like growth factor I. In branchial epithelia, development and differentiation of the seawater-type chloride cell (and their underlying biochemistry) is regulated by GH, IGF-I, and cortisol, whereas the freshwater-type chloride cell is regulated by prolactin and cortisol. In the epithelia of gastrointestinal tract, prolactin induces cell proliferation during freshwater adaptation, whereas cortisol stimulates both cell proliferation and apoptosis. We propose that control of salinity acclimation in teleosts by prolactin and growth hormone primarily involves regulation of cell proliferation, apoptosis, and differentiation (the latter including upregulation of specific ion transporters), and that there is an important interaction of these hormones with corticosteroids.

Keywords: Prolactin; Growth hormone; Fish; Osmoregulation

1. Introduction

Prolactin and growth hormone form a family of pituitary polypeptide hormones that share a common structure. They belong to a super-family of cytokines and produce their biological effects by interacting and dimerizing with single transmembrane-domain receptors. These hormones and their receptors are thought to have arisen as a result of gene duplication and subsequent divergence early in vertebrate evolution (Forsyth and Wallis, 2002). One of the earliest known functions of prolactin in teleost fish was its role in ion uptake. More recently, growth hormone has also been shown to have a role in teleost osmoregulation, in addition to its growth promoting role.

All teleost fish maintain the osmotic concentration of their extracellular fluid at approximately one-third the osmotic strength of seawater. In freshwater the kidney produces a dilute urine to counteract diffusive water gains, while the gill actively takes up ions. In seawater diffusive water loss is counteracted by drinking seawater and actively taking up salts and water across the gut, while the gill actively secretes salts through chloride cells (also known as mitochondrion-rich cells). Gill chloride cells with different transporters and slightly different morphology may also be the site of ion uptake in freshwater (Hiroi et al., 2005). Several recent reviews provide detailed evidence for the cellular and biochemical mechanisms for salt and water transport in teleosts (Evans et al., 2005; Marshall, 2002).

Due to the osmoregulatory strategy of teleost outlined above, teleost fish face osmotic challenges in both freshwater and seawater, and to an even greater degree when moving between these environments. The requirements for salt and water homeostasis in freshwater or seawater can be quite large due to the large respiratory surface area of the gill. When demands for oxygen uptake increase blood perfusion and decrease perfusion distance in the gill there is an

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accompanying increase in diffusive water and ion movements (the osmorespiratory compromise). There is also a critical acclimation response in most teleosts following changes in external salinity that is the basis for their ability to move between freshwater and seawater. Hormones involved in maintaining or expanding the capacity of water and ion transport are required both for maintenance of homeostasis within any given aquatic environment and following changes in salinity.

In this review, our goal is to summarize recent findings on the osmoregulatory actions of prolactin and growth hormone, and to integrate them into a physiological relevant view of the role of these hormones in ion homeostasis and salinity acclimation in teleost fish.

2. Prolactin

The importance of prolactin is evident from wide spectrum of functions it performs in vertebrates (Bole-Feysot et al., 1998; Harris et al., 2004; Sakamoto et al., 2003). Grace Pickford was the first to conclusively demonstrate that prolactin has a role in ion uptake mechanisms of teleost fish in freshwater (Pickford and Phillips, 1959). Since then, evidence for prolactin as a freshwater adapting hormone in fish comes from studies on exogenous prolactin treatment and prolactin dynamics in freshwater and euryhaline fish, including ours using salmonids, goldfish, cichlid fishes (tilapia), and mudskipper where the homologous prolactins and their receptors are identified and assays for their quantification have been developed.

Gene expression, synthesis, secretion, and plasma levels of prolactin increase following freshwater exposure (Manzon, 2002). Metabolic clearance rate of prolactin in salmonids are also increased following freshwater acclimation (Ogasawara et al., 1996; Sakamoto et al., 1991). In teleosts, at least in tilapia, plasma factors such as osmolality and cortisol importantly exert direct regulatory actions on PRL secretion. As in mammals, however, a specific prolactin-releasing factor, prolactin-releasing peptide, has recently been identified in teleosts. Although there remains significant controversy over the physiological relevance of the PRL-releasing bioactivity described for the peptides, especially in rats, we have reported for teleosts that PrRP promoted specifically PRL transcription and secretion, with the histochemical localization of PrRP neuronal terminals near PRL cells in the pituitaries (Sakamoto et al., 2003). Moreover, PrRP seems to be an essential stimulator of PRL since antiserum to PrRP decrease PRL levels (Fujimoto et al., 2006). In the amphibious euryhaline mudskipper, the localization of mRNA levels of PrRP and PRL as well as their regulation during acclimation to different environments are closely related. The brain–pituitary axis of PrRP–PRL operates during both terrestrial and freshwater (FW) acclimation. In addition, the axis in the gut mucus cells is activated during FW acclimation (Sakamoto et al., 2005a,b). This possible presence of the PrRP–PRL axis in teleost peripheral organs might suggest an ancient history of this axis prior to the evolution of the hypothalamus–pituitary, and it is possible that the PrRP is an original, fundamental regulator of PRL. During phylogeny, with an increasing functional diversity of PRL, its regulators may have also become more diverse. In the course of evolutionary time, PrRP in some species may have lost its original PRL-releasing functions and become "free" to evolve new functions. In mammals, finally, the PrRP–PRL axis might be diminishing even in the hypothalamus–pituitary.

Prolactin treatment primarily reduces ion and water permeability of osmoregulatory surfaces (Hirano, 1986). In gastrointestinal tract of euryhaline fish, PRL generally decreases NaCl and water absorption by reducing the permeability of the epithelium, although there is species variability (Manzon, 2002). On the other hand, cortisol increases ion and water permeability as well as active uptake of ions, especially chloride transport, which increases the osmotic uptake of water (Loretz, 1995). Cortisol is also suggested to be required to regulate ion and water movement across the intestinal epithelium of freshwater fish (Hirano et al., 1975). Additionally, GH stimulates Na-dependent proline absorption in coho salmon intestine (Collie and Stevens, 1985).

Although prolactin has also been shown to have sodium and chloride retaining activity in a variety of freshwater and euryhaline teleosts, there is surprising little information on the cellular and biochemical effectors of the osmoregulatory actions of prolactin. Prolactin has been shown to affect chloride cells, both by inhibiting the development of seawater chloride cells (Herndon et al., 1991) and promoting the morphology of ion uptake cells (Pisam et al., 1993). Cortisol also has a role in promoting ion uptake and 'freshwater type' chloride cells in several teleosts (Perry and Goss, 1994). Although an interaction between prolactin and cortisol in controlling freshwater acclimation has been proposed (McCormick, 2001), there is as yet little direct evidence for this hypothesis. In hypophysectomized channel catfish, prolactin, and cortisol together cause a greater elevation of plasma ions that either hormone alone (Eckert et al., 2001). Zhou et al. (2003) observed that cortisol and prolactin together had a greater effect than either hormone alone in promoting the transepithelial resistance and potential of an in vitro gill cell preparation. The recent findings that there is a 'mineralocorticoid' in fish (see Prunet, this volume) opens up even greater complexities for the interaction of cortisol and prolactin in controlling ion regulation.

3. Growth hormone

Smith (1956) was the first to observe that growth hormone treatment could increase the capacity of fish (brown trout, *Salmo trutta*) to tolerate exposure to seawater. It was later determined that this effect was due to the capacity of this hormone to increase the number and size of gill chloride cells, Na^+,K^+-ATPase, and the Na^+,K^+,$2Cl^-$ cotransporter (NKCC), ion transporters involved in salt secretion (McCormick, 2001; Pelis and McCormick, 2001). Cortisol

also has the capacity to affect chloride cells and these transporters, and there is an important additive/synergistic interaction between cortisol and growth hormone (Madsen, 1990). Some of the interaction of GH and cortisol may be through GH's capacity to upregulate the number of gill cortisol receptors (Shrimpton and McCormick, 1998). The effect of GH on salinity tolerance and differentiation of salt secretory mechanisms is not restricted to salmonids, as this effect has been found in two other euryhaline species, tilapia and killifish (Sakamoto et al., 1997; Mancera and McCormick, 1999).

Some of the actions of growth hormone are through 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, and killifish (Mancera and McCormick, 1998). In brown trout, long term IGF-I treatment can increase the number of gill chloride cells and Na^+,K^+-ATPase activity concurrent with increased salt secretory capacity (Seidelin et al., 1999). Prior in vivo GH treatment of coho salmon increase the in vitro capacity of IGF-I to increase ATPase activity (Madsen and Bern, 1993). Seidelin et al. (1999) have also demonstrated an additive interaction of IGF-I and cortisol on gill chloride cells and Na^+,K^+-ATPase, similar to the interaction between GH and cortisol.

In addition to the effects of exogenous hormones treatments, changes in pituitary gene expression, secretion, circulating levels, and metabolic clearance rate of growth hormone also provides evidence for the osmoregulatory actions of growth hormone in several euryhaline species widely separated in the evolution (Sakamoto et al., 1993). Plasma GH levels have also been found to increase in stenohaline catfish following exposure to 12 ppt seawater (Drennon et al., 2003). Shepherd et al. (2005) have found that the circulating levels of IGF-I increases following exposure of rainbow trout to seawater. These authors also found an increase in the circulating levels of the 21-, 42-, and 50-kDa IGF-I binding proteins after seawater exposure. In addition to circulating levels of 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 (Sakamoto and Hirano, 1993). IGF-I has been found specifically in gill chloride cells whose number and/or size are stimulated by growth hormone (Sakamoto et al., 2001). In the research cited above there is evidence for both an endocrine and autocrine/paracine action of the IGF-I in the teleost gill. In mammals it appears that both endocrine and paracrine actions of IGF-I are important in regulating growth, and a similar pattern may exist for the osmoregulatory actions of IGF-I in teleost fish.

Growth hormone receptors have been found in the liver, gill, gut, and kidney (Fukada et al., 2004; Kajimura et al., 2004; Lee et al., 2001; Nakao et al., 2004; Sakamoto and Hirano, 1991; Tse et al., 2003). We also found that the occupancy of growth hormone receptors increased following exposure to seawater (Sakamoto and Hirano, 1991). Growth hormone has also been detected in osmoregulatory organs and may be acting in an autocrine or paracrine manner in these tissues (Sakamoto et al., 2005a,b; Yang et al., 1999). Specific high affinity, low capacity IGF-I receptors have been found in gill tissue of salmon and tilapia (McCormick, unpublished results), and have been immunocytochemically localized to gill chloride cells in striped bass (Christian Tipsmark, personal communication). The influence of salinity on GH and IGF-I receptor numbers and what endocrine factors may be regulating them in different osmoregulatory tissues has yet to be examined.

The GH/IGF-I axis is also important in the preparatory physiological adaptations that comprise the parr-smolt transformation of anadromous salmonids. This transformation includes a number of changes that are adaptive for seawater entry, including increased salinity tolerance. Underlying increased salinity tolerance during smolting are increases in gill chloride cell size and number, Na,K-ATPase activity, NKCC levels as well as changes in the gut and kidney (Hoar, 1988). Circulating levels of GH and IGF-I increase during smolting and are responsive to photoperiod and temperature cues that also alter the timing of increased salinity tolerance (McCormick et al., 2002). Exposure of Atlantic salmon smolts to estrogenic compounds results in decreased circulating levels of IGF-I (but not GH or cortisol), which likely mediates ability of these compounds to decrease salinity tolerance (McCormick et al., 2005).

To date a relatively small number of teleosts have been examined for the physiological impact of the GH/IGF-I axis on osmoregulation. Exogenous treatments have been found to affect most salmonids, tilapia, and killifish. Evidence from circulating hormones, local production, and from salmonids provides convincing evidence for endocrine and paracrine actions of the GH/IGF-I axis, but there is relatively little information in this area from other teleosts. However, there is no apparent effect of exogenous GH on several osmoregulatory parameters in the gilthead sea bream (*Sparus auratus*) (Mancera et al., 2002), and osmoregulatory effects on the another sea bream, *Sparus sarba*, are not consistent with a seawater acclimating impact (Kelly et al., 1999). Pituitary GH and liver IGF-I mRNA levels in sea bream were lower after exposure to both hyper- and hyposaline conditions (Deane and Woo, 2004). Similarly, GH may not play an osmoregulatory role in the eel (Sakamoto et al., 1993). Sea bream and eel have marine origins or a limited capacity to hyperosmoregulate. Species variation linked to different limitations in ion regulatory capacity and/or strategies for ion regulation may affect whether and to what extent the GH/IGF-I axis is involved in osmoregulation. A similar situation may occur for prolactin; we might expect to see no large effect of prolactin in stenohaline seawater teleosts (e.g., anglerfish and pipefish with aglomerular kidneys) where any ion uptake may be maladaptive. More research on both euryhaline and stenohaline species are necessary to determine how widespread the osmoregulatory actions of prolactin and the GH/IGF-I

axis are among teleost fish, and what phyletic histories and evolutionary pressures have acted to bring about any observed patterns. Relative importance of extrapituitary PRL/GH should also be noted, since high extrapituitary expressions have been reported only in teleosts (Imaoka et al., 2000; Sakamoto et al., 2005a,b) and production of PRL may have been centralized into pituitary during terrestrial tetrapod evolution.

4. Common features of prolactin and growth hormone action (Fig. 1)

In seawater-adapted euryhaline fish, the permeability of the gastrointestinal tract is generally greater than that of freshwater-adapted fish. The esophageal epithelium of seawater fish is simple columnar, whereas that of freshwater fish is stratified. In the anterior intestine (esophagus) of mudskipper, the increased apoptosis throughout the entire epithelium during seawater acclimation appears to be important for the simple epithelium and subsequent high permeability, whereas cell proliferation induced randomly throughout the epithelium during freshwater acclimation appears to be important for the development of stratified epithelium and subsequent low permeability; proliferating cells are located at the troughs of the intestinal folds in seawater and apoptotic cells are located around the tips of the intestinal folds in freshwater (Sakamoto, unpublished). In euryhaline teleosts during adaptation to different salinities, indeed, the adaptive modifications in the structures of gastrointestinal tracts correlate the changes in their permeabilities as well as in the expressions or activities of transporters and pumps. For example, seawater acclimations of eel induce the intestinal Na^+,K^+-ATPase and aquaporin (Aoki et al., 2003; Collie and Bern, 1982; Cutler et al., 2000; Hirano and Mayer-Gostan, 1976; Yamamoto and Hirano, 1978). In the intestine of the euryhaline goby, prolactin and cortisol induces cell proliferation during freshwater adaptation, whereas cortisol stimulates apoptosis via glucocorticoid receptors during seawater adaptation. Although thyroid-hormone inducible apoptosis of the metamorphosing amphibian tail is inhibited by PRL, the thyroid hormone shows no significant effects on cell turnover in the goby intestine (Sakamoto, unpublished) (see (Fig. 1)).

The control of cell turnover and differentiation is also likely to be a critical process controlling chloride cells and salinity acclimation in the teleost gill. Though the specific morphologies can vary among teleosts, secretory type chloride cells (usually with a deep apical pit) increase during SW acclimation, and uptake type chloride cells (usually with a broad apical region with microvilli) increases during freshwater acclimation. The number of these cells can be increased through three mechanisms: proliferation and differentiation of new cells, differentiation (or transformation) of existing chloride cells from one type to another, and a decrease in cell death (necrosis or apoptosis). Differentiation will involve increases in specific transporters, in the case of salt secretory cells Na^+,K^+-ATPase, the $Na^+,K^+,2Cl^-$ cotransporter and the apical CFTR chloride channel (McCormick et al., 2003; Hiroi et al., 2005). By controlling these mechanisms of cell turnover and differentiation, growth hormone, prolactin, and cortisol have the capacity to govern chloride cells and the acclimation

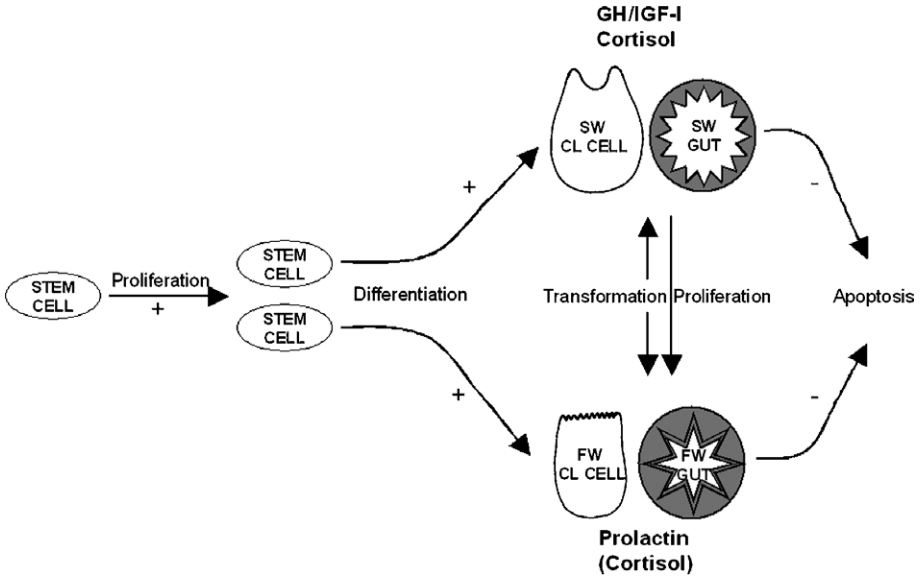

Fig. 1. Summary representation of the epithelial differentiation in the gill and gut of euryhaline teleosts during acclimation to different salinities. In the gut during SW acclimation, cortisol induces apoptosis and proliferating cells become localized in troughs of intestinal folds, resulting in the high permeability. During FW acclimation, PRL stimulates cell proliferation synergistically with cortisol, and apoptosis becomes localized at their tips, resulting in low permeability. In the gill, coordinated changes in proliferation, differentiation, transformation and apoptosis result in increased ion uptake chloride cells in freshwater and increased salt secretory chloride cells in seawater. The GH/IGF-I and cortisol axes interact to increase salt secretory chloride cells, and prolactin and cortisol interact to increase ion uptake chloride cells, but the cell turnover pathways through which these hormones control gill chloride cells has not been examined.

response of the teleost gill. To date, however, we have only indirect evidence for a specific role of these hormones in proliferation, differentiation and apoptosis. Cortisol in vitro can increase size and Na^+,K^+-ATPase activity of chloride cells, but only maintains their numbers (McCormick, 1990), suggesting that by itself cortisol controls differentiation but not proliferation. Short-term treatment of freshwater fish with GH and IGF-I can increase salinity tolerance prior to detectable increases in gill Na^+,K^+-ATPase, but prevents decreases in gill Na^+,K^+-ATPase seen after seawater exposure (Mancera and McCormick, 1999; McCormick, 1996). This suggests that GH and IGF-I provide a protective effect, perhaps by preventing apoptosis of secretory chloride cells thereby maintaining salt secretory capacity of the gill. This effect would be consistent with the known anti-apoptotic effects of IGF-I in many mammalian tissues (Vincent and Feldman, 2002). Since GH and IGF-I also have effects on proliferation and differentiation of many cell types, including cartilage, muscle and embryonic cells of fish (Castillo et al., 2004; Pozios et al., 2001), their impact on cell proliferation in osmoregulatory tissue may be anticipated. The GH/IGF-I axis is known to play a role in normal and injury-induced renal hypertrophy of mammals (Rabkin and Schaefer, 2004), but to our knowledge GH and IGF-I actions in cell proliferation of osmoregulatory organs in basal vertebrates has not been examined.

On the goldfish scales, PRL expanded the mucous cell layers, which may restrict efficiently water inflow by the mucous system (Fujimoto et al., 2006). Throughout vertebrates, a large proportion of the various actions of PRL seem to be associated directly or indirectly with cell proliferation and/or apoptosis (Sakamoto et al., 2005a,b). One of the major targets is the epithelium such as keratinocytes (Girolomoni et al., 1993), skin melanocytes, and prostate epithelial cells (Duncan and Goldman, 1985; Sage, 1970). Beyond the epithelia, our other data confirm that control of cell turnover are also the important functions of PRL in teleosts. PRL_{177} (and GH) stimulated thymidine incorporation by tilapia ceratobranchial cartilage (Shepherd et al., 1997). Furthermore, prolactin specifically inhibited the osteoclastic activities of goldfish scales and promoted osteoblastic activities in vitro (Suzuki1 et al., 2005). Many of these are seen in lower vertebrates, but recent data confirm that cell proliferation and/or inhibition of apoptosis are also the important functions of PRL in mammals (Bole-Feysot et al., 1998).

Thus, one of PRL/GH's primary functions in osmoregulation may be the control of cell turnover in osmoregulatory epithelia. We anticipate a major focus of our future understanding the hormonal control of the salinity acclimation process in fish will be to determine how prolactin, growth hormone, IGF-I, and cortisol interact to control cell turnover and differentiation processes in tissues involved in salt and water transport. Further research using this reversible system of cell turnover should be intriguing when we compare with the irreversible regulations in development, metamorphosis, and growth.

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