CHAPTER TWELVE

Hormonal regulation of aquaporins in fishes

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Abstract

Comparative studies over the last two decades have revealed that fishes leverage aquaporins (AQPs) to facilitate the movements of water, small non-ionic solutes, and gases across cell membranes. Accordingly, AQPs are expressed in tissues responsible for maintaining hydromineral balance of the whole organism. In teleost fishes, threats to hydromineral balance imposed by fluctuations in environmental salinity are met with the activation of multiple endocrine axes. This chapter first discusses recent advances in our understanding of how hormones control the expression of AQPs in tissues that support hydromineral balance, namely the gastrointestinal tract, kidney, and gill. The second objective of this chapter is to review how hormones regulate teleost AQPs in support of fluid transport processes underlying the production of gametes specialized for release into aquatic environments.

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1. Introduction

The study of how organisms control the movements of solutes and water at the macromolecular, cellular, and tissue levels constitutes a fundamental line of biological inquiry. To reach a nuanced understanding of how vertebrate osmoregulatory systems operate in adaptive, as well as pathological states, physiologists must illuminate how intrinsic regulators, such as hormones of the endocrine system, control the activities of effectors of solute and water transport. Since fishes inhabit a varied array of aquatic (and semi-aquatic) habitats that pose formidable challenges to hydromineral balance, they represent powerful systems from which to develop mechanistic models of how homeostasis of the internal milieu is maintained. From an ecological perspective, salinity is among the most important physical characteristics of aquatic environments that govern the distribution of species (Whitehead, Roach, Zhang, & Galvez, 2011). Thus, the operation and control of osmoregulatory systems within fishes is inextricable from their patterns of evolution and ecological specialization.

Aquaporins (AQPs) constitute a superfamily of integral membrane proteins that facilitate passive movements of water, small non-ionic compounds, and gases across cell membranes (Cerdà & Finn, 2010). Vertebrate AQPs are assigned into distinct groups based upon their permeation preferences: classical aquaporins (AQP0, -1, -2, -4, -5, and -6), aquaglyceroporins (AQP3, -7, -9, and -10), aquaporin 8 (AQP8), and unorthodox aquaporins (AQP11 and -12). While fishes do not have orthologs of mammalian AQP2, -5, and -6, they possess a larger number of total AQPs in comparison to mammals as a result of tandem and genomic duplication events that occurred during their evolution (Finn & Cerdà, 2011; Finn, Chauvigné, Hlidberg, Cutler, & Cerdà, 2014; Madsen, Engelund, & Cutler, 2015). The evolution, structure-function relationships, and tissue-expression patterns of piscine AQPs have been extensively reviewed previously (Cerdà & Finn, 2010; Finn & Cerdà, 2011; Hillyard, 2015; Madsen et al., 2015; Tingaud-Sequeira et al., 2010). This chapter intends to complement these reviews by outlining our current understanding of the endocrine regulation of piscine AQPs.

Fishes are traditionally classified into three classes: Agnatha (jawless fishes), Chondrichthyes (cartilaginous fishes), and Osteichthyes (bony fishes). The vast majority of investigations into the hormonal regulation of piscine AQPs have utilized teleost models (class Osteichthyes; subclass

Actinopterygii; infraclass Neopterygii; division Teleostei) (Moyle & Cech, 2004). The ensuing discussion reflects this fact and primarily describes the endocrine regulation of teleost AQPs. This chapter begins by broadly introducing the tissues that support hydromineral balance in teleost fishes prior to describing how particular hormones control their activities. This is followed by a discussion of how hormones control AQPs expressed within epithelia of the esophagus, intestine, kidney, and gill. This chapter concludes with an outline of how endocrine control of gonadal AQPs underlies the production of teleost eggs and sperm before proposing avenues for future investigation.

2. Teleost strategies to maintain hydromineral balance

The majority of teleost fishes maintain internal conditions at roughly one-third the osmotic strength (270–400 mOsm) of seawater (SW) (Evans & Claiborne, 2008). Teleosts residing in freshwater (FW) are therefore in constant risk of both excessive hydration and salt loss across body surfaces. FW-acclimated teleosts counter this situation by excreting water via dilute urine while actively absorbing ions (Na^+, Cl^-, Ca^{2+}) from the external environment and the diet across branchial and gastrointestinal epithelia, respectively (Evans, Piermarini, & Choe, 2005; Guh, Lin, & Hwang, 2015; Kaneko, Watanabe, & Lee, 2008). Marine teleosts, on the other hand, must excrete ions gained by passive diffusion from the surrounding SW. Teleosts cannot produce urine that is hyperosmotic to body fluids as a means to conserve water because their renal tubules lack the Loop of Henle (Nishimura & Fan, 2003). To fend off dehydration, marine teleosts drink SW to replace water that is lost via osmosis to the external environment. Imbibed SW is desalinated by the esophagus to produce a fluid closer to the osmolality of plasma (Hirano & Mayer-Gostan, 1976). Then, the intestine partakes in fluid uptake through solute-linked transport processes (Grosell, 2014). Water is conserved by reabsorption across the urinary bladder (Hirano, Johnson, Bern, & Utida, 1973). Finally, the gills and kidney actively secrete monovalent (Na^+, Cl^-) and divalent ions (Mg^{2+}, Ca^{2+}, and SO_4^{2-}), respectively (Kaneko et al., 2008).

While the vast majority of teleosts inhabit a single aquatic environment characteristic of either FW or SW, a relatively small percentage of species (~5%) can thrive in waters that range between FW (≤0.5‰) and SW (30–40‰) conditions (Schultz & McCormick, 2013). These "euryhaline" teleosts tolerate a wide range of salinities because of their evolved capacities to modulate or reverse salt and water transport pathways in the gill, kidney,

gut, and urinary bladder (Kültz, 2015). This plasticity is mediated, in part, by the endocrine system that orchestrates the activities of these various tissues (Takei & McCormick, 2013). In turn, euryhaline fishes are intensively studied to resolve how hormones modulate the functions of osmoregulatory tissues at the molecular level. Nearly all of the studies investigating the hormonal control of piscine AQPs have been conducted with euryhaline species.

3. Hormonal control of osmoregulation in teleost fishes

Hormones are central players in the homeostatic regulation of salt and water balance. Perturbations of internal osmotic conditions, caused by changes in environmental salinity, elicit the secretion of hormones that orchestrate the expression, localization, and function of sub-cellular effectors of solute and water transport (Seale, Watanabe, & Grau, 2012). These effectors include AQPs, ion channels, co-transporters, exchangers, and Na^+/K^+-ATPases (Breves, McCormick, & Karlstrom, 2014; McCormick, 2001; Takei, Hiroi, Takahashi, & Sakamoto, 2014). The actions of established "osmoregulatory hormones" are outlined below to provide context for the ensuing discussion of their demonstrated or putative control of AQPs.

3.1 Prolactin

Among the hormones secreted from the teleost pituitary, prolactin is considered the "FW-adapting hormone" because it promotes survival in dilute waters by stimulating ion-conserving and water-excreting processes operating in the gill, kidney, gut, and urinary bladder (Hirano, 1986; Pickford & Phillips, 1959). Accordingly, both *prolactin* gene expression and prolactin hormone release are directly stimulated by reductions in extracellular/plasma osmolality (Fuentes, Brinca, Guerreiro, & Power, 2010; Yada, Hirano, & Grau, 1994); the signal transduction mechanisms underlying these responses have been extensively studied (Seale et al., 2012). Based on the broad range of tissues known to respond to prolactin across teleosts, it is widely believed that prolactin is a highly-conserved stimulator of adaptive processes in dilute environments (Hirano, 1986; McCormick, 2001). Only more recently, however, actual molecular targets of prolactin have been identified which underlie discreet solute transporting processes (Breves et al., 2014).

3.2 Growth hormone

Growth hormone (GH) secreted from the anterior pituitary is regarded as a "SW-adapting hormone" because it promotes the survival of teleosts in hyperosmotic environments. This activity is well established in salmonids (Sakamoto & McCormick, 2006; Sakamoto, McCormick, & Hirano, 1993), whereas evidence in non-salmonid fishes is far more limited. Contrasting with the regulation of prolactin, the release of GH from the pituitary is stimulated by increases in extracellular/plasma osmolality (Nilsen et al., 2008; Seale, Fiess, Hirano, Cooke, & Grau, 2006; Seale et al., 2002). GH directly controls ion extrusion through branchial ionocytes expressing its cognate receptor, and indirectly through systemic (liver derived) and/or locally produced insulin-like growth-factor 1 (IGF1) (Seidelin, Madsen, Byrialsen, & Kristiansen, 1999). Information in non-salmonids regarding the direct effects of IGF1 on hyposmoregulatory mechanisms is especially scarce (Mancera & McCormick, 1998). While GH is likely pleiotropic in its support of SW acclimation, it is largely unknown whether it regulates intestinal and renal functions despite the robust expression of its receptor in these tissues (Björnsson, 1997; Fukada et al., 2004).

3.3 Cortisol

Cortisol, which operates as both a mineralocorticoid and a glucocorticoid in teleosts, is produced by interrenal tissue under the control of adrenocorticotropic hormone (Mommsen, Vijayan, & Moon, 1999). Cortisol is typically deemed a "SW-adapting hormone" because it directly stimulates the activities and/or expression of Na^+/K^+-ATPases and ion transporters tied to ion extrusion pathways in the gill; cortisol also acts indirectly by synergizing with GH/IGF1 signaling (McCormick, 2001). Synergism with other factors is a theme of cortisol action in fishes (Mommsen et al., 1999), and interestingly, cortisol can promote FW acclimation by acting alone or in concert with prolactin (McCormick, 2001). Collectively, the patterns of circulating prolactin, GH, and cortisol in response to changes in salinity (Kajimura et al., 2004; Nilsen et al., 2008; Yada et al., 1994), and the expression of their receptors in osmoregulatory tissues, are in strong agreement with their indispensability to survival in FW and/or SW.

3.4 Additional "osmoregulatory hormones"

There is no question that a far broader collection of hormones beyond the "classical" osmoregulatory hormones outlined above underlies

hydromineral balance in teleosts (Guh et al., 2015; Takei et al., 2014). Very few of these factors have been implicated in the regulation of teleost AQPs, and therefore, only a small number of them will appear in this chapter. The neurohypophyseal hormones, arginine vasotocin (AVT) and isotocin, are the teleost homologs to mammalian vasopressin and oxytocin, respectively. AVT has been considered a possible mediator of hyposmoregulation by marine fishes given the antidiuretic action of vasopressin in mammals. Moreover, cortisol may enhance AVT signaling by stimulating the expression of its receptor in target tissues (Cádiz et al., 2015). However, hypothalamic *avt* gene expression and plasma AVT levels exhibit species-dependent responses to changes in salinity, making it difficult to ascribe a universal osmoregulatory function to AVT in teleosts (Takei et al., 2014). A similar scenario has emerged for isotocin because it stimulates either hyposmoregulation or hyperosmoregulation in species-dependent fashions (Chou, Hung, Wu, Hwang, & Hwang, 2011; Martos-Sitcha et al., 2013; Takei et al., 2014). Parathyroid hormone-related protein (PTHrP), a calciotropic hormone expressed in multiple tissues (Guerreiro, Renfro, Power, & Canario, 2007), regulates intestinal water absorption in at least one euryhaline model, the sea bream (*Sparus aurata*), and may therefore regulate intestinal AQPs (Carvalho, Gregório, Canário, Power, & Fuentes, 2015).

4. Endocrine control of AQPs in osmoregulatory tissues

4.1 AQPs in the gastrointestinal tract

4.1.1 Esophagus

To fend off dehydration in SW environments, segments of the gastrointestinal tract must work in concert to sustain solute-linked water absorption. Teleosts inhabiting marine environments drink SW as a necessary source of water. However, to enable water absorption, the imbibed SW (~1000 mOsm) must be desalinated to ~500 mOsm prior to its passage to the stomach (Grosell, 2014). Na^+ and Cl^- are moved from the luminal fluid into blood plasma by active and passive transport; Na^+ and Cl^- are subsequently excreted by branchial ionocytes (Hirano & Mayer-Gostan, 1976; Kaneko et al., 2008; Takei et al., 2017). To effectively reduce the osmolality of the luminal fluid, the osmotic permeability of the esophageal epithelium must be low. Accordingly, in euryhaline Japanese eel (*Anguilla japonica*), esophageal *aqp1* and *-3* mRNA levels are down regulated in SW-acclimated animals (Takei et al., 2017). Whether AQP1 and -3 are

expressed in apical and/or basolateral membrane of epithelial cells stands unresolved; nonetheless, the regulated expression of these AQPs could underlie the low osmotic permeability in the esophagus that enables the desalination of SW (Hirano & Mayer-Gostan, 1976). Cortisol seems to be a plausible regulator of AQP1 and -3 given its response to salinity challenges and promotion of SW tolerance (McCormick, 2001). However, in the only study to date that investigated esophageal AQP responses to cortisol, cortisol actually stimulated *aqp1a* mRNA in silver European eels (*A. anguilla*) preparing for downstream migration (Martinez et al., 2005). Interestingly, SW exposure induced *GH receptor* gene expression in Atlantic salmon (*Salmo salar*) esophagus (J.P. Breves, unpublished), a response paralleling elevated plasma GH levels (Nilsen et al., 2008). While highly speculative, GH may support SW tolerance by modulating solute and/or water handling processes in the esophagus. In any case, while the regulation of *aqps* following SW exposure suggest they underpin adaptive functions of the esophagus, a clearer picture of their endocrine control awaits further studies.

4.1.2 Intestine

In marine environments, desalinated SW from the esophagus passes through the stomach where it subsequently enters the anterior intestine at ~400 mOsm (Grosell, 2014). Upon entering the intestine, monovalent ions and water are absorbed from the luminal fluid. Both transcellular and paracellular routes contribute to net fluid transport; AQPs offer a means by which transcellular osmotic permeability can be enhanced (Madsen et al., 2015; Sundell & Sundh, 2012). This notion was supported by the identification of intestinal AQPs/*aqps* that were up regulated in euryhaline fishes, such as sea bream (*S. aurata* and *S. sarba*), sea bass (*Dicentrarchus labrax*), European eel, Japanese eel, Atlantic salmon, and mummichog (*Fundulus heteroclitus*), during SW acclimation (Aoki et al., 2003; Deane, Luk, & Woo, 2011; Engelund et al., 2013; Giffard-Mena et al., 2007; Jung et al., 2015; Kim, Watanabe, Kaneko, Huh, & Park, 2010; Lignot, Cutler, Hazon, & Cramb, 2002; Madsen et al., 2011; Martinez et al., 2005b; Raldúa, Otero, Fabra, & Cerdà, 2008; Tipsmark, Sorensen, & Madsen, 2010). In support of acclimation to SW, cortisol stimulates intestinal fluid uptake (Hirano & Utida, 1968; Utida et al., 1972). A link between cortisol and AQP1/*aqp1* was first shown in both yellow and silver European eels when 8-day cortisol implants stimulated AQP1 levels in mucosal scrapes of whole intestine (Martinez et al., 2005b). Similarly, cortisol-implanted sea

bream showed elevated *aqp1* levels in the intestine (Deane et al., 2011). It is noteworthy that in these two instances cortisol stimulated AQP1/*aqp1* in animals inhabiting hyposmotic environments. In other words, a hyperosmotic external environment coupled with the presence of desalinated SW in the gastrointestinal tract was not required for cortisol to stimulate AQP1. In some instances (see the discussion of branchial AQP3/*aqp3*), environmental salinity can exert an overriding effect on hormonal regulators of AQPs.

While intestinal AQP1/*aqp1* is generally increased following SW exposure in teleosts (Madsen et al., 2015), it is curious that black porgy (*Acanthopagrus schlegeli*) and Japanese medaka (*Oryzias latipes*) do not fit this pattern (An, Kim, & Choi, 2008; Madsen, Bujak, & Tipsmark, 2014). These species challenge the "dogma" of intestinal water transport such that paracellular, rather than transcellular, pathways may dominate (Madsen et al., 2014). It is probable that AQP1/*aqp1* sensitivity to cortisol, and perhaps to other hormones, in porgy and medaka would contrast with the patterns reported in eel and sea bream.

In preparation for their migration from FW to marine habitats, many salmonids undergo smoltification, a developmental phase that entails the acquisition of phenotypes supporting hyposmoregulation (Hoar, 1988). Coinciding with springtime elevations in plasma cortisol, Atlantic salmon smolts increase their capacity for intestinal fluid absorption (Specker, 1982; Sundell et al., 2003; Veillette, White, & Specker, 1993). When considering the stimulatory action of cortisol on fluid transport capacities (Cornell, Portesi, Veillette, Sundell, & Specker, 1994; Veillette, Sundell, & Specker, 1995) along with the dynamic *aqp1a, -1b, -8b,* and *-10* expression patterns which occur seasonally and/or following SW exposure in smolts (Tipsmark, Sorensen, & Madsen, 2010), Atlantic salmon are a fitting model for identifying how connections between cortisol and AQPs underlie life-stage transitions. Moreover, Atlantic salmon provide an opportunity to probe whether the elevated plasma GH levels in smolts (Björnsson, 1997) play a role in "pre-adapting" the intestine for fluid uptake by controlling AQPs. While Tipsmark, Sorensen, Hulgard, and Madsen (2010) proposed that stimulation of *claudin-25b* mRNA levels by GH may favor solute and water absorption, no published studies have described any effects of GH on AQPs.

There is some evidence that AVT may regulate AQPs in support of intestinal fluid uptake. AQP1a/*aqp1a* and AQP1b/*aqp1b* are highly expressed in sea bream anterior intestine and rectum, respectively (Raldúa et al., 2008). AVT stimulated swelling by *Xenopus* oocytes expressing the AVT receptor

(V2-type) in combination with AQP1a or -1b (Martos-Sitcha, Campinho, Mancera, Martínez-Rodríguez, & Fuentes, 2015). Isotocin stimulated swelling via AQP1a, but not AQP1b, in oocytes expressing the isotocin receptor. While regulatory links between AVT, isotocin, and AQP1a/-1b await confirmation in intact sea bream, the *in vitro* activities of AVT and isotocin indicate capacities for stimulating AQP-mediated fluid absorption.

Euryhaline teleosts must down regulate processes appropriate to marine environments (e.g., intestinal fluid uptake) upon entering FW environments. In SW, HCO_3^- is secreted into the lumen of the intestine by enterocytes to produce Ca^{2+} and Mg^{2+} carbonate aggregates. The formation of these aggregates enhances water absorption by lowering the osmolality of the luminal fluid (Grosell, 2014). *In vitro* treatment with PTHrP inhibits HCO_3^- secretion and water absorption by sea bream intestine (Carvalho et al., 2015). Intact sea bream injected with the PTHrP receptor agonist, PTHrP(1–34), showed reduced *aqp1b* mRNA levels in the anterior intestine. Accordingly, *aqp1b* levels were stimulated by the PTHrP receptor antagonist, PTHrP(7–34) (Carvalho et al., 2015). Thus, PTHrP inhibits fluid uptake via the regulation of AQP1b and HCO_3^- secretion (Carvalho et al., 2015). In parallel with the adjustments to intestinal physiology that are made upon FW-entry, drinking must also be attenuated to avoid excessive hydration. In this regard, PTHrP further down regulates processes suited to marine environments by inhibiting drinking (Guerreiro et al., 2001). In addition to reducing intestinal Na^+, Cl^-, and fluid absorption (Morley, Chadwick, & El Tounsy, 1981; Utida et al., 1972), prolactin, like PTHrP, also inhibits intestinal HCO_3^- secretion (Ferlazzo et al., 2012), and thus an inhibitory action of prolactin on intestinal AQPs should be investigated. In eel, the intestinal hormone guanylin is secreted from goblet cells to affect ion and water metabolism (Takei & Yuge, 2007). For example, guanylin inhibited water absorption and short-circuit current in intestinal sacs prepared from SW-acclimated Japanese eel (Ando, Wong, & Takei, 2014; Yuge, Inoue, Hyodo, & Takei, 2003). Investigations into the potential for guanylin to repress AQP expression/function are warranted in light of guanylin inhibiting solute-linked water transport via $Na^+/K^+/2Cl^-$-cotransporter 2β (Ando et al., 2014).

4.2 AQPs in the kidney and urinary bladder

In order to support systemic water balance, the functional control of renal AQPs in fishes should align with the excretion of water in FW environments

(via dilute urine) and/or the conservation of water in SW environments (Engelund & Madsen, 2011; Madsen et al., 2015). While renal AQP/*aqp* expression is highly responsive to salinity (Engelund & Madsen, 2011; Madsen et al., 2015), only a few studies have investigated hormonal control of renal AQPs (Deane et al., 2011; Martinez et al., 2005a). An 8-day cortisol infusion inhibited *aqp1aa* and *aqp1ab* mRNA levels in yellow European eels (Martinez et al., 2005a). Given that renal *aqp1aa* and *aqp1ab* levels are diminished when yellow eels are acclimated to SW versus FW (Martinez et al., 2005a), this finding is consistent with cortisol promoting phenotypes associated with SW acclimation. While precise roles for AQP1s in teleost nephrons are not defined, their apparent down regulation following SW exposure and cortisol treatment indicates they underlie water secretion by FW-acclimated fish (Engelund & Madsen, 2011). The finding that cortisol affected *aqp1* mRNA levels in eel was particularly noteworthy given the scant information on how cortisol affects renal activities in teleosts (Takei & McCormick, 2013).

In mammals, vasopressin plays an essential role in preventing dehydration by regulating AQP2 in renal collecting ducts (Valenti & Tamma, 2016). Interestingly, two studies have correlated *aqp* expression with AVT signaling in fish kidney. In black porgy, *aqp1* and *AVT receptor* mRNA levels are positively correlated in salinities ranging from FW to SW (An et al., 2008). In aestivating African lungfish (*Protopterus annectens*), the kidney supports the retention of body water in desiccated environments. When compared with lungfish inhabiting FW, aestivating lungfish showed concurrent elevations in *AVT* and *aqp0* mRNA expression in the hypothalamus and kidney, respectively (Konno, Hyodo, Yamaguchi, Matsuda, & Uchiyama, 2010). Importantly, Konno et al. (2010) demonstrated that lungfish *aqp0* encodes a functional water channel. Thus, regulatory systems linking vasopressin/AVT-family hormones with AQPs to support survival under terrestrial conditions are probably not restricted to tetrapods, and seemingly also operate in lungfishes.

The urinary bladder is an osmoregulatory tissue in teleosts exhibiting permeabilities to Na^+, Cl^-, and water generally above those found in tetrapod bladders (Bently, 1987). In euryhaline mudsucker (*Gillichthys mirabilis*) and flounder (*Platichthys* sp.), Na^+ and water are transported across urinary bladder epithelium at higher rates when fish are acclimated to SW versus FW (Hirano, Johnson, & Bern, 1971; Hirano et al., 1973). The reabsorption of water by the bladder reduces the amount of SW that must be ingested (and the associated salt load) to maintain water balance (Howe & Gutknecht, 1978).

There is no available information on whether AQPs are expressed in fish urinary bladder; thus, it stands entirely unresolved whether AQPs underlie water movement across this tissue. Cortisol and prolactin may activate and repress AQP expression/function, respectively, given their effects on Na^+ and water reabsorption at the tissue level (Doneen, 1976; Hirano et al., 1971). It will be important to investigate the hormonal regulation of AQPs in appropriate models because not all euryhaline species exhibit salinity-dependent capacities for water reabsorption by the urinary bladder (Hirano et al., 1973).

4.3 AQPs in the gill

The extensive surface area (up to 90% of the total body surface area) of teleost gills enables exchanges with the external environment that are necessary for hydromineral and acid-base balance (Evans et al., 2005). These exchanges occur via a suite of functionally distinct ionocytes (mitochondrion-rich cells) harbored in the gill that are specialized for Na^+, Cl^-, K^+, and Ca^{2+} transport (Dymowska, Hwang, & Goss, 2012; Evans et al., 2005). The coordination of ionocyte differentiation and proliferation, along with gene and protein expression within ionocytes, underlies the functional plasticity of branchial epithelium in euryhaline species (Dymowska et al., 2012; Kültz et al., 2007; McCormick, 2001).

Branchial AQP/*aqp* levels are correlated with environmental salinity and rapidly change following fluctuations in salinity (Cutler & Cramb, 2002; Lema, Carvalho, Egelston, Kelly, & McCormick, 2018; Lignot et al., 2002; Madsen et al., 2014; Moorman, Lerner, Grau, & Seale, 2015; Tipsmark, Sorensen, & Madsen, 2010; Tse, Au, & Wong, 2006; Whitehead, 2010). This is especially true for the aquaglyceroporin, AQP3 (Cutler, Martinez, & Cramb, 2007; Madsen et al., 2015). For example, in eel and Mozambique tilapia (*Oreochromis mossambicus*), *aqp3* levels were markedly reduced following transfer from FW to SW, whereas transfer from SW to FW induced *aqp3* levels (Breves et al., 2016; Cutler & Cramb, 2002; Lignot et al., 2002; Watanabe, Kaneko, & Aida, 2005). These patterns of *aqp3* regulation within euryhaline species imply that AQP3 has deleterious functions under SW conditions. Indeed, Whitehead et al. (2011) proposed that patterns of *aqp3* expression diverged by adaptive evolutionary mechanisms among mummichog populations distributed along salinity gradients. While additional *aqp* transcripts beyond *aqp3*, such as *aqp1a, -1b*, *-10*, and *-11*, also display salinity-dependent expression in salmon and medaka gill (Kim, Kim, Kim, Lee, & Nam, 2014; Tipsmark, Sorensen, & Madsen, 2010), the extent to which their expression is salinity-dependent in other euryhaline species is unknown.

A clear picture of how AQPs support adaptive functions in the gill remains elusive. Transepithelial water movement appears unlikely on the basis that branchial water exchange is disadvantageous for fish in both FW and SW environments (Cerdà & Finn, 2010). In rainbow wrasse (*Coris julis*) and eel, AQP3-immunoreactivity was observed in the extensive basolateral tubular system of ionocytes (Brunelli et al., 2010; Lignot et al., 2002). In turn, Cutler and Cramb (2002) and Tipsmark, Sorensen, and Madsen (2010) proposed that AQP3 enables efficient regulatory cell volume control upon salinity changes. Interestingly, mammalian sperm expressing mutated AQP3 fail to regulate cell volume when exposed to hyposmotic conditions (Chen & Duan, 2011). To tolerate variations in salinity, branchial cells in contact with the ambient environment must possess means for osmotic stress signaling (Kültz et al., 2007). AQP3 may permit cells to swell or shrink depending upon fluctuations in extracellular osmolality. Changes in cell volume can then couple with signal transduction pathways underlying the control of effectors of ion transport (Breves et al., 2016; Inokuchi et al., 2015; Watanabe et al., 2005). In a similar fashion, AQP3 plays a well-characterized role in mediating osmoreception in prolactin-secreting cells of the tilapia pituitary (Watanabe, Hirano, Grau, & Kaneko, 2009). It certainly cannot be discounted that AQP3 may mediate glycerol, urea, and/or ammonia transport by branchial cells (Cutler & Cramb, 2002; Lignot et al., 2002). While the functional role(s) for branchial AQPs remain unclear, this has not precluded investigations into whether hormones underlie their salinity-dependent expression patterns.

Cortisol was the first hormone shown to affect the branchial expression of an *aqp* transcript. FW-acclimated eels infused with cortisol showed a marked decrease in the expression of *aqp3* mRNA in the gill while intestinal *aqp3* levels were not affected (Cutler et al., 2007). Choi et al. (2013) subsequently reported that cortisol diminished branchial *aqp3* and -8 mRNAs in sockeye salmon (*Oncorhynchus nerka*) parr and smolts. These patterns suggest that elevated plasma cortisol following transfer from FW to SW is responsible, at least in part, for the concurrent attenuation of *aqp3* levels (Cutler & Cramb, 2002; Cutler et al., 2007; Mommsen et al., 1999). With cortisol established as a key controller of the SW phenotype (low AQP3), there remained no identified controller of the FW phenotype (elevated AQP3).

Plasma prolactin levels spike in euryhaline tilapia within several hours after transfer from SW to FW. Prolactin then plateaus at levels still elevated from those observed in SW-acclimated animals (Kajimura et al., 2004; Yada et al., 1994). The coincident increases in plasma prolactin and branchial

AQP3/*aqp3* that occur during FW acclimation motivated the application of hypophysectomy and hormone replacement (Nishioka, 1994) to assess whether prolactin signaling directs AQP3/*aqp3* expression. Hypophysectomy blocked the increase in *aqp3* expression that accompanies FW acclimation and reduced AQP3-immunoreactivity in ionocytes, goblet cells, and pavement cells (Breves et al., 2016). Replacement with prolactin rescued the inability of hypophysectomized animals to increase AQP3/*aqp3* upon exposure to FW. Prolactin similarly stimulated AQP3/*aqp3* expression in filaments co-incubated with prolactin *in vitro*. Interestingly, prolactin did not stimulate *aqp3* in SW-acclimated tilapia, while co-administration with cortisol blocked the effect of prolactin both *in vivo* and *in vitro*. Recall that cortisol and prolactin can be synergistic in their support of FW phenotypes (McCormick, 2001). This is decidedly not the case with respect to controlling AQP3. Thus, a complex interplay between prolactin, cortisol, and ambient salinity works to tightly-regulate branchial AQP3 expression.

With prolactin identified as a regulator of tilapia AQP3, it is interesting to consider the generality of this link. Prolactin signaling is essential for Mozambique tilapia to maintain osmotic balance in FW (Dharmamba & Maetz, 1972). By contrast, coho salmon (*Oncorhynchus kisutch*) and rainbow trout (*Salmo gairdneri*) maintain osmotic balance in FW following hypophysectomy (Björnsson & Hansson, 1983; Björnsson, Yamauchi, Nishioka, Deftos, & Bern, 1987). These contrasting dependencies upon the pituitary suggest that branchial phenotypes associated with FW are not regulated in the same fashion across teleost clades. Since there is consensus that AQP3/*aqp3* expression is generally increased under FW conditions (Cutler et al., 2007; Madsen et al., 2015), it will be interesting to learn whether salmonids exhibit a prolactin-AQP3 connection.

5. Endocrine control of AQPs during gamete production

Thus far this chapter has focused on the endocrine control of AQPs within tissues that mediate hydromineral balance of the organism; AQPs also underlie the production of teleost gametes. Eggs of marine teleosts encounter strong osmotic gradients upon their release into SW. AQP1 is indispensable to the adaptive physiologies that eggs leverage to minimize dehydration in hyperosmotic environments (Cerdà, Zapater, Chauvigné, & Finn, 2013; Chauvigné, Zapater, & Cerdà, 2011). The eggs of marine teleosts undergo hydration during final maturation. Hydration occurs because of the accumulation of osmolytes and lipids within the oocyte along with enhanced

osmotic permeability of the plasma membrane (Fabra et al., 2006). Fabra, Raldúa, Power, Deen, and Cerda (2005) demonstrated that insertion of AQP1ab into the outer membrane is necessary for egg hydration in sea bream; Kagawa et al. (2011) subsequently implicated AQP1b in the hydration of eel eggs. In sea bream, transcription of the *aqp1ab* gene is stimulated by progesterone receptors bound by the progestin, 17α,20β-dihydroxy-4-pregnen-3-one (17,20β-P) (Zapater, Chauvigné, Tingaud-Sequeira, Finn, & Cerdà, 2013). Accordingly, the promoter of the *aqp1ab* gene contains two progestin responsive elements (Zapater et al., 2013). 17,20β-P is synthesized in granulosa cells under the control of follicle-stimulating hormone (FSH) during oocyte differentiation/early growth stage. Kagawa et al. (2011) further proposed that estradiol and IGF1, synthesized within ovarian follicles, may promote the regulation of AQP1 in post-translational fashions. By contrast, zebrafish (*Danio rerio*) eggs are not hydrated prior to their release into FW environments, and therefore, *aqp1b* is not highly expressed in the ovary (Tingaud-Sequeira et al., 2008). Interestingly, even though they are released into FW, catfish (*Heteropneustes fossilis*) eggs are hydrated (Singh & Joy, 2010) and ovarian *aqp1b* expression is elevated during the pre-spawning phase (Chaube et al., 2010). AVT stimulated *aqp1b* levels in incubated catfish ovarian follicles, leading Chaube et al. (2010) to propose a novel role for AVT in egg hydration.

In teleosts, AQPs support spermatogenesis, spermiation, sperm motility, and participate in controlling the composition of seminal fluid in the spermatic duct (Boj, Chauvigné, & Cerdà, 2015; Chauvigné et al., 2018; Chauvigné et al., 2011; Zilli et al., 2009). In sea bream testis, hormonal control of AQP/*aqp* expression varies depending upon the developmental stage of the tissue (Boj, Chauvigné, Zapater, & Cerdà, 2015). The enhanced expression of AQP1ab/*aqp1ab* during the resting phase is mediated by FSH and luteinizing hormone (LH) through the production of testosterone. Contrasting with its regulation in oocytes (Zapater et al., 2013), *aqp1ab* is not regulated by 17,20β-P in testis. During spermatogenesis and/or spermiation, AQP0a/*aqp0a*, -1aa/*-1aa*, -7/-7, *-8b*, *-9b*, and 10b/*-10b* are stimulated by FSH and/or LH through androgenic pathways (Boj, Chauvigné, Zapater, & Cerdà, 2015). Collectively, these patterns demonstrate that tight temporal regulation of multiple AQPs underlies fluid transport necessary for sperm production. It was recently revealed that nine AQPs are expressed in the spermatic duct of sea bream where they presumably support the further maturation and nourishment of sperm (Chauvigné et al., 2018). Whether hormones regulate AQPs in the spermatic duct is

unknown; estrogens and progestins are candidates given their activities in mammalian spermatic duct (Chauvigné et al., 2018).

6. Concluding remarks

Basal vertebrates have proven to be powerful model systems within the discipline of comparative physiology. Agnathans, such as the sea lamprey (*Petromyzon marinus*), offer opportunities to consider how endocrine and osmoregulatory systems operate in basal vertebrates (Ferreira-Martins, Coimbra, Antunes, & Wilson, 2016; Kawauchi & Sower, 2006). The lamprey endocrine system reflects a condition that preceded the diversification of several hormone families and their receptors within the vertebrate lineage. For instance, lamprey possess only a single factor within the GH/prolactin/somatolactin-family of pituitary hormones. While this factor was designated GH in part because it stimulated hepatic *igf1* gene expression (Kawauchi et al., 2002), there is no information on whether it regulates osmoregulatory processes. Moreover, Close, Yun, McCormick, Wildbill, and Li (2010) proposed that 11-deoxycortisol is a mineralocorticoid (and a glucocorticoid) that promotes the SW tolerance of lamprey. By assessing the activities of these factors on lamprey AQPs (Finn et al., 2014), light can be shed on the extent to which hormones are linked with AQPs in extant members of basal vertebrate clades.

Another area for future study is to resolve how hormones underlie the expression of AQPs during early development. In mummichog embryos, AQP3 underlies water and solute transport processes that support the avoidance of dehydration and/or the acceleration of development following aerial exposure (Tingaud-Sequeira, Cerdà, Zapater, Chauvigné, & Otero, 2009). In zebrafish embryos, AQP1a1 is expressed in epidermal ionocytes where it regulates cell volume and/or water flux into the circulation (Kwong, Kumai, & Perry, 2013). Horng, Chao, Chen, Shih, and Lin (2015) reported that AQP1a1 facilitates water and CO_2 diffusion into a sub-type of ionocytes (HR cells) specialized for H^+ secretion. AQP1a1 knockdown decreased H^+ secretion by HR cells (Horng et al., 2015) as well as CO_2 and ammonia excretion by whole embryos (Talbot, Kwong, Gilmour, & Perry, 2015). Collectively, these studies demonstrate that AQPs confer critical physiological functions during early development. Embryonic endocrine systems are highly sensitive to osmoregulatory challenges and respond in fashions that promote homeostasis of the whole organism (Chou et al., 2011; Hoshijima & Hirose, 2007; Liu et al., 2006). With epidermal ionocytes

already well-established targets of hormones (Guh et al., 2015), zebrafish are highly appropriate models to reveal how hormones regulate the activities of AQPs in a developmental context.

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