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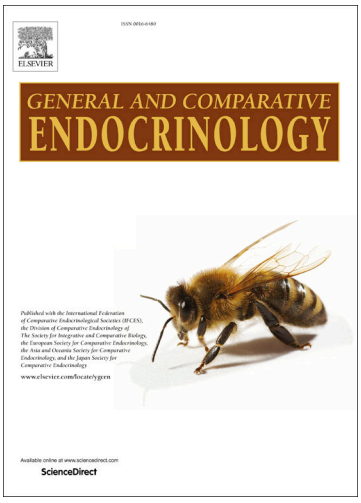

Minireview

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Mini-Review

Osmoregulatory actions of prolactin in the gastrointestinal tract of fishes

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Abstract:

In fishes, Prl signaling underlies the homeostatic regulation of hydromineral balance by controlling essential solute and water transporting functions performed by the gill, gastrointestinal tract, kidney, urinary bladder, and integument. Comparative studies spanning over 60 years have firmly established that Prl promotes physiological activities that enable euryhaline and stenohaline teleosts to reside in freshwater environments; nonetheless, the specific molecular and cellular targets of Prl in ion- and water-transporting tissues are still being resolved. In this short review, we discuss how particular targets of Prl (e.g., ion cotransporters, tight-junction proteins, and ion pumps) confer adaptive functions to the esophagus and intestine. Additionally, in some instances, Prl promotes histological and functional transformations within esophageal and intestinal epithelia by regulating cell proliferation. Collectively, the demonstrated

actions of Prl in the gastrointestinal tract of teleosts indicate that Prl operates to promote phenotypes supportive of freshwater acclimation and to inhibit phenotypes associated with seawater acclimation. We conclude our review by underscoring that future investigations are warranted to determine how growth hormone/Prl-family signaling evolved in basal fishes to support the gastrointestinal processes underlying hydromineral balance.

Highlights: ► Prl regulates gastrointestinal processes supportive of hydromineral balance. ► Prl receptors are expressed in esophagus and intestine of fishes. ► Prl directs the expression of intestinal solute transporters in euryhaline teleosts. ► Agnathans will provide insight into how Gh/Prl-family hormone function evolved.

Keywords: hydromineral balance; euryhaline; hormone; teleost; esophagus; intestine

1. Introduction

Pituitary hormones regulate many of the physiological systems that vertebrates utilize to maintain homeostasis. In species spanning the vertebrate lineage, the peptide hormone prolactin (Prl) coordinates critical aspects of hydromineral balance, reproduction, lactation, growth, metabolism, and immunity (Bole-Feysot et al., 1998; Freeman et al., 2000). Fishes are conventionally classified into three classes: Agnatha (jawless fishes), Chondrichthyes (cartilaginous fishes), and Osteichthyes (bony fishes). Among teleost fishes (class Osteichthyes; subclass Actinopterygii; infraclass Neopterygii; division Teleostei), Prl was first recognized in mummichog (*Fundulus heteroclitus*) as an essential “freshwater (FW)-adapting hormone” (Pickford and Phillips, 1959). Since then, decades of research have firmly established that Prl exerts highly conserved actions on teleost osmoregulatory organs, namely the gill, kidney, intestine, integument, and urinary bladder, to promote ion-conserving and water-secreting processes. Here, our intent is to complement prior reviews (Bern, 1983; Breves et al., 2014; Collie and Hirano, 1987; Hirano, 1986; Loretz and Bern, 1982; Manzon, 2002; Power, 2005; Sakamoto and McCormick, 2006) by concentrating on the molecular and cellular targets of Prl within the gastrointestinal tract of fishes.

Hydromineral balance is contingent upon the tight control of solute and water movements at the molecular, cellular, and organismal levels. Perturbations in internal osmotic conditions caused by drops in environmental salinity directly elicit the secretion

of Prl from the rostral pars distalis (Ingleton et al., 1973; Kwong et al., 2009; Sage, 1968;
70 Seale et al., 2012). Accordingly, elevations in *prl* gene expression and plasma Prl levels occur when euryhaline teleosts encounter marked reductions in environmental salinity
72 (Fuentes et al., 2010; Lee et al., 2006a; Seale et al., 2012; Shepherd et al., 1999; Yada et al., 1994). In stenohaline FW-species (e.g., zebrafish (*Danio rerio*)), Prl signaling is
74 activated when animals are exposed to 'ion-poor' conditions (Hoshijima and Hirose, 2007; Liu et al., 2006). Through systemic circulation, Prl directs the expression,
76 localization, and/or function of macromolecular mediators of hydromineral balance in target tissues (Breves et al., 2014; Manzon, 2002; Seale et al., 2012). Moreover, Prl may
78 simultaneously dampen ionoregulatory processes appropriate to seawater (SW) acclimation that would otherwise be deleterious to euryhaline fish inhabiting FW
80 (Seidelin and Madsen, 1997).

Upon binding to Prl receptors (Prlrs), Prl activates dimerization and cross-
82 phosphorylation events that activate Jak/Stat, MAPK, PI3K, and/or Src signaling pathways (Bole-Feysot et al., 1998; Freeman et al., 2000; Horseman and Gregerson,
84 2013). Teleost Prlrs share highly conserved functional domains with other vertebrate Prlrs, including an extracellular ligand-binding domain, a single-pass transmembrane
86 region, and a Box 1 region (Bole-Feysot et al., 1998; Fiol et al., 2009; Huang et al., 2007; Pierce et al., 2007; Prunet and Auperin, 1994; Prunet et al., 2000; Sandra et al.,
88 1995). In fishes, Prl binding was initially characterized in the gill, kidney, liver, gonad, and intestine of Mozambique tilapia (*Oreochromis mossambicus*) (Dauder et al., 1990;
90 Edery et al., 1984; Fryer, 1979). More recently, it was revealed that teleosts possess multiple *prlr* gene loci (Huang et al., 2007). The two distinct encoded Prlrs, denoted Prlr1
92 and -2, control the expression of distinct target genes upon ligand binding (Chen et al., 2011; Fiol et al., 2009; Huang et al., 2007). The plasticity of *prlr1* and *-2* gene expression
94 in osmoregulatory organs during salinity acclimation seemingly provides a mechanism to modulate tissue sensitivity to circulating Prl (Breves et al., 2011; Fiol et al., 2009; Flores
96 and Shrimpton, 2012; Pierce et al., 2007; Tomy et al., 2009).

Growth hormone (Gh) and cortisol, the traditional "SW-adapting hormones" in
98 teleosts, promote the survival of animals in hyperosmotic environments in part by antagonizing the actions of Prl (McCormick, 2001; Seidelin and Madsen, 1997). The
100 widespread expression of the Gh receptor (Ghr) suggests that Gh is pleiotropic in its support of SW acclimation; however, exactly how Gh regulates osmoregulatory systems
102 is largely unknown (Björnsson, 1997; Reindl and Sheridan, 2012). Cortisol is widely

accepted as a “SW-adapting hormone” because it directly stimulates the activities and/or expression of Na^+/K^+-ATPase (NKA) and ion transporters linked with ion extrusion and fluid uptake capacities in the gill and intestine, respectively (Cornell et al., 1994; Hirano and Utida, 1968; Utida et al., 1972; Veillette et al., 1995). Cortisol also indirectly promotes SW acclimation by synergizing with Gh/insulin-like growth factor signaling (McCormick, 2001). In some instances, cortisol may promote FW acclimation by acting alone, or in concert, with Prl (Jackson et al., 2005; McCormick, 2001).

2. Gastrointestinal functions and hydromineral balance: an overview

Because the majority of teleosts typically maintain internal conditions between 270-400 mOsm/kg, fish inhabiting FW environments are at constant risk of both excessive hydration and the diffusive loss of ions across body surfaces (Evans and Claiborne, 2008). In turn, FW-acclimated teleosts simultaneously excrete water via dilute urine and actively absorb ions (Na^+, Cl^-, Ca^{2+}) from both the external environment and their diet across branchial and gastrointestinal epithelia, respectively (Evans et al., 2005; Guh et al., 2015; Kaneko et al., 2008). Teleosts in marine environments, on the other hand, must excrete ions gained through passive diffusion and combat dehydration by continuously drinking ambient SW. The drinking rates of euryhaline fishes are thus markedly greater in marine versus FW-environments (Carrick and Balment, 1983; Fuentes and Eddy, 1997; Hirano, 1974; Lin et al., 2002; Malvin et al., 1980; Perrott et al, 1992). As a necessary source of water, imbibed SW is processed by multiple segments of the gastrointestinal tract that work in concert to sustain solute-linked water absorption. Imbibed SW is first desalinated to ~500 mOsm/kg by the esophagus, a process which produces a fluid closer to the osmolality of plasma (Grosell, 2014; Hirano and Mayer-Gostan, 1976). Na^+ and Cl^- are moved from the luminal fluid into blood plasma by active and passive transport and are subsequently extruded by branchial ionocytes (Hirano and Mayer-Gostan, 1976; Kaneko et al., 2008; Takei et al., 2017). Desalinated SW from the esophagus then passes through the stomach where some additional desalination may occur prior to entering the anterior intestine at ~400 mOsm/kg (Grosell, 2014). The stomach exhibits similar rates of Na^+ and Cl^- uptake in SW- and FW-acclimated fishes (Hirano and Mayer-Gostan, 1976). Upon entering the intestine, monovalent ions and water are absorbed from the luminal fluid through both transcellular and paracellular routes (Madsen et al., 2015; Sundell and Sundh, 2012). In SW-acclimated/marine fishes, HCO_3^- is secreted by enterocytes into the lumen of the intestine to produce Ca^{2+} and

Mg^{2+} carbonate aggregates. The formation of these aggregates enhances water
138 absorption by lowering the osmolality of the luminal fluid (Grosell, 2014). For a comprehensive coverage of solute and water handling by the teleost gastrointestinal
140 tract we direct readers to previous reviews (Grosell, 2006; Loretz, 1995, Sundell and Sundh, 2012; Whittamore, 2012).

142 Despite decades of sustained research on the osmoregulatory actions of Prl in fishes, a detailed picture of the mechanisms underlying these actions has remained
144 largely undeveloped due to limitations in our understanding of how ions and water are transported across osmoregulatory epithelia. The identification of Prl-regulated
146 mediators (e.g., ion transporters and channels, NKA subunits, Ca^{2+}-ATPases, aquaporins (Aqps), and tight-junction proteins) of ion and water transport within
148 branchial epithelium (Breves et al., 2014, 2017; Flik et al., 1996) suggests that teleosts will serve as tractable models from which to also determine how Prl operates
150 mechanistically in extrabranchial sites (e.g., kidney, urinary bladder, and gastrointestinal tract). It is toward this objective that we highlight recent findings and specify emerging
152 themes for future study.

154 **3. Prolactin action on gastrointestinal functions**

3.1 Esophagus

156 Effective osmoregulatory strategies entail the controlled entry of external fluids into the gastrointestinal tract. Hormonal regulation of drinking behavior in fishes is
158 conventionally attributed to “fast-acting” hormones (e.g., angiotensin II and atrial natriuretic peptides) as opposed to Gh/Prl-family peptides (Takei et al., 2014). While the
160 administration of Prl affected drinking rates in rats (Kaufman, 1981), to our knowledge, Prl has not been directly linked with anti-dipsogenic responses that could guard against
162 excessive hydration in FW environments.

The esophageal epithelium undergoes functional and histological changes in
164 response to variations in environmental salinity (Meister et al., 1983). For instance, the transfer of SW-acclimated Japanese eel (*Anguilla japonica*) to FW resulted in reduced
166 Na^+ and Cl^- permeability via the transformation of a simple columnar epithelium into a stratified epithelium (Yamamoto and Hirano, 1978). Increased cell proliferation (PCNA-
168 positive nuclei) within the esophageal epithelium of Mozambique tilapia undergoing FW acclimation coincided with increases in plasma Prl and esophageal *prlr* gene expression
170 (Takahashi et al., 2007). Nile tilapia (*Oreochromis niloticus*), which cannot readily

tolerate salinities >25‰ (Watanabe et al., 1985), did not exhibit discernable differences in the esophagus following salinity changes (Cataldi et. al., 1988). The coincident activation of Prl signaling with esophageal remodeling in Mozambique tilapia provided indirect evidence for a link between Prl and esophageal phenotypes associated with FW acclimation (Takahashi et al., 2007). Supporting evidence for a link between Prl and esophageal remodeling was provided when Prl stimulated cell proliferation within explants of Japanese medaka (*Oryzias latipes*) esophagus (Takahashi et al., 2013). Given their responses to salinity challenges, Prl, Gh, and/or cortisol may control additional characteristics of the esophagus such as mucosal vascularization (Cataldi et al., 1987; McCormick, 2001). In mammals, Prl (and Prl fragments termed vasoinhibins) regulates angiogenesis depending on the physiological context (Clapp et al., 2006), but to date, no links have been made between Gh/Prl-family peptides and vascularization of teleost esophagus. Apoptosis underlies the stratification of esophageal epithelium during SW acclimation, and accordingly, treatment with Gh or cortisol increased the presence of TUNEL-positive nuclei in medaka esophagus (Takagi et al., 2011; Takahashi et al., 2013). Together, Prl, Gh, and cortisol exert activities (as mitogenic or apoptotic factors) in the esophagus consistent with their established roles in teleost osmoregulation. Future studies are now required to better resolve comparative patterns of esophageal Gh/Prl-family hormone receptor expression in euryhaline teleosts.

3.2 Intestine

3.2.1 Prolactin receptors

It was first reported that Prl administration affected intestinal Na^+, Cl^-, and fluid absorption in rainbow trout (*Oncorhynchus mykiss*) and Japanese eel (Morley et al., 1981; Utida et al., 1972). Consistent with these functional observations, Prl binding and Prlr immunoreactivity were observed within the intestinal epithelium of rainbow trout and gilthead sea bream (*Sparus aurata*), respectively (Morley et al., 1981; Santos et al., 2001). *prlr* genes are expressed in the intestine of Nile and Mozambique tilapia (Fiol et al., 2009; Pierce et al., 2007; Sandra et al., 1995, 2000, 2001; Zhang et al., 2010), Japanese pufferfish (*Takifugu rubripes*) (Lee et al., 2006a, 2006b), gilthead and black sea bream (*Spondyliosoma cantharus*) (Huang et al., 2007; Santos et al., 2001), rainbow trout (Rouzic et al., 2001), goldfish (*Carassius auratus*) (Tse et al., 2000), mangrove killifish (*Kryptolebias marmoratus*) (Rhee et al., 2010), Japanese flounder (*Paralichthys olivaceus*) (Higashimoto et al., 2001), blue discus (*Symphysodon aequifasciata*) (Khong

et al., 2009), turbot (*Scophthalmus maximus*) (Liu et al., 2020), and zebrafish (Breves et al., 2013). Recall that teleosts express two *prlr* genes (*prlr1* and *-2*). In Nile tilapia, *prlr1* expression is higher in the posterior intestine versus the anterior intestine and *prlr1* expression in the anterior intestine was increased following a reduction in environmental salinity (Sandra et al., 2000, 2001). In contrast, *prlr2* expression was higher in the anterior intestine of Mozambique tilapia acclimated to SW versus FW (Seale et al., 2014). This pattern paralleled the elevated *prlr2* expression in other tissues following the transfer of FW-acclimated fish to SW (Fiol et al., 2009; Seale et al., 2012). It is important to note that particular studies did not report dynamic *prlr* expression in the intestine following salinity changes (Fiol et al., 2009; Lee et al., 2006b). Going forward, the intestine may serve as an appropriate organ from which to resolve how the multiple Prlrs mediate distinct and/or overlapping physiological responses to circulating Prl. While zebrafish cannot tolerate a broad range of salinities, as a model they do offer conditional gene mutagenesis as a means to analyze the functions of two *prlrs* expressed in the intestine (Burg et al., 2018). It must also be acknowledged that Prl plays pivotal roles in immunity (Harris and Bird, 2000). Since the intestinal epithelium constitutes a barrier between the organism and the environment, intestinal *prlr* expression may also enable immunomodulatory activities that are independent from aspects of ion and water balance (Yada et al., 2002).

3.2.2 Cell proliferation

Salinity-induced changes in the morphology of the intestinal epithelium resemble those of the esophageal epithelium; in FW-acclimated mudskipper (*Periophthalmus modestus*), Nile tilapia, and Japanese eel the intestinal epithelium is typically stratified with expanded folds, while in SW/brackish water (BW)-acclimated animals the epithelium is thinner and columnar (Takahashi et al., 2006b; Tran-Ngoc et al., 2017; Yamamoto and Hirano, 1978). As in the esophagus (Takagi et al., 2011; Takahashi et al., 2013), enhanced cell proliferation (and decreased apoptosis) during FW acclimation underlies the development of stratified intestinal epithelium with reduced permeability (Takahashi et al., 2006b). In mudskipper, Prl stimulated cell proliferation, without affecting apoptosis, in the intestinal epithelium of animals acclimated to BW (10‰) (Takahashi et al., 2006a). From a comparative perspective, these findings align with the plethora of Prl actions identified within fishes and other vertebrates that involve the promotion of cell proliferation (Sakamoto and McCormick, 2006). In mammals, Prl stimulated cell

proliferation within the gut (Bujanover et al., 2002; Mainoya, 1978) in addition to various organs such as mammary glands, skin, vascular smooth muscle, pancreas, brain, and lymph nodes (Bole-Feysot et al., 1998; Freeman et al., 2000; Hennighausen and Robinson, 2005).

3.2.3 $Na^+/K^+/2Cl^-$ cotransporter 2 and Na^+/K^+-ATPase

In SW-acclimated/marine teleosts, the intestine mediates solute-linked water uptake via a suite of ion transporters, channels, and pumps (Grosell, 2006; Sundell and Sundh, 2012). For example, apically located $Na^+/K^+/2Cl^-$ cotransporter 2 (Nkcc2) mediates the entry of Na^+ and Cl^- into the interior of enterocytes prior to their subsequent transport across the basolateral membrane (Whittamore, 2012). Accordingly, *nkcc2* expression in the anterior intestine increased in several species following their exposure to SW (Esbaugh and Cutler, 2016; Gregório et al., 2013; Li et al., 2014; Ruhr et al., 2016; Watanabe et al., 2011; Zhang et al., 2019). Albeit based on a limited number of studies, intestinal Nkcc2 appears to be under hormonal control. Arginine vasotocin (Avt) inhibited the bumetanide-sensitive absorptive current of gilthead sea bream intestine mounted in Ussing chambers (Martos-Sitcha et al., 2013). Accordingly, arginine vasopressin (Avp), the mammalian homolog to Avt, diminished distal colonic ion absorption in mice by inhibiting the insertion of Nkcc2 into the apical membrane (Xue et al., 2014). Renoguanylin and guanylin also inhibited Nkcc2-mediated ion transport in gulf toadfish (*Opsanus beta*) and Japanese eels, respectively (Ando et al., 2014; Ruhr et al., 2016). Because Prl promotes phenotypes associated with FW acclimation and it was reported that Prl administration reduced intestinal Na^+, Cl^-, and fluid absorption in Japanese eel and rainbow trout (Morley et al., 1981; Utida et al., 1972), one would predict that Prl exerts similar inhibitory actions on Nkcc2. Paradoxically, Prl actually stimulated *nkcc2* expression in hypophysectomized Mozambique tilapia (Seale et al., 2014). This pattern may reflect the fact that Mozambique tilapia exhibit greater solute and water uptake in the anterior intestine when acclimated to FW (Mainoya, 1982), making them an exception to the stereotypical pattern of enhanced intestinal solute and water transport in SW-acclimated fishes. Future investigations should examine Prl control of Nkcc2 in models shown to exhibit enhanced solute-linked water transport under SW conditions (e.g., Atlantic salmon, mummichog, sea bream, and Japanese eel) to further assess the relationship between Prl and Nkcc2.

The NKA enzyme is a ubiquitously expressed ion pump consisting of three

subunits (α, ß, and γ) responsible for energizing active transport by key osmoregulatory organs as well as maintaining Na^+ and K^+ gradients across all cell membranes. Varied effects of Prl on branchial and renal NKA activity have been reported in teleosts (Manzon, 2002), and similarly, there is not a clear picture of how Prl regulates intestinal NKA. For example, Prl stimulated NKA activity in the intestine of silver sea bream (*Sparus sarba*) (Kelly et al., 1999) and climbing perch (*Anabas testudineus*) (Peter et al., 2014), whereas other studies reported no effect of Prl on NKA activity or *NKA α-subunit* gene expression in FW- or BW-acclimated fishes (Pickford et al., 1970; Seale et al., 2014; Seidelin and Madsen, 1999). The functions of the regulatory γ-subunit of the NKA enzyme, or Fxyd, in teleosts are becoming better resolved (Saito et al., 2010; Tipsmark, 2008; Wang et al., 2008; Yang et al., 2013). Fxyd proteins modify the transport properties of NKA by binding to the α-subunit; thus, given the dynamics of intestinal NKA activity during salinity acclimation (Sundell and Sundh, 2012), it is highly plausible that Prl will emerge as a regulator of intestinal Fxyd proteins. While Prl inhibited *fxyd-11*/Fxyd-11 in salmon and tilapia gill (Tipsmark et al., 2010a, 2011), *fxyd-11* is not highly expressed in the intestine (Yang et al., 2013). Thus, *fxyd* isoforms more robustly expressed in the intestine (e.g., medaka *fxyd-5*, *-9*, and *-12*) may offer better targets for probing Prl-Fxyd links underlying intestinal function.

3.2.4 Na^+/HCO_3^- cotransporters and carbonic anhydrase

SW-acclimated/marine fishes secrete HCO_3^- into the intestinal lumen to support fluid absorption (Alves et al., 2019; Grosell, 2011). Intestinal HCO_3^- secretion is regulated by multiple endocrine factors with contrasting activities. For example, HCO_3^- secretion is stimulated by stanniocalcin and guanylin, yet inhibited by parathyroid hormone-related protein, renoguanylin, and Prl (Ferlazzo et al., 2012; Fuentes et al., 2010; Ruhr et al., 2018; Takei et al., 2019). The transit of HCO_3^- through enterocytes involves basolateral entry of HCO_3^- from the blood plasma by a Slc4-type Na^+/HCO_3^- cotransporter (Nbce1) followed by apical exit into the intestinal lumen via a Slc26-type Cl^-/HCO_3^- exchanger (Kurita et al., 2008). Another source of HCO_3^- for apical secretion comes from the intracellular hydration of CO_2 by carbonic anhydrase (Grosell, 2006; Grosell et al., 2009). Ferlazzo et al. (2012) showed that Prl inhibited *in vitro* secretion of HCO_3^- in explants of gilthead sea bream anterior intestine. Accordingly, chemical inhibitors of transduction pathways linked with Prl signaling (Jak2, Mek, and PI3K) disrupted Prl-stimulated HCO_3^- secretion (Ferlazzo et al., 2012). A dose-dependent

inhibitory effect of Prl occurred in the absence of basolateral HCO_3^- within 20 min; thus, Prl seemingly targeted the intracellular generation and subsequent secretion of HCO_3^-. There is currently no information on whether Prl affects the expression or activity of carbonic anhydrase, but this enzyme should now be viewed as a putative target of Prl given its role in intracellular HCO_3^- generation. Interestingly, Prl also reduced the gene expression of *slc4a4* (Ferlazzo et al., 2012), potentially affecting the basolateral acquisition of HCO_3^- from blood plasma. Prl, therefore, emerges as a potential regulator of HCO_3^- secretion through multiple mechanisms.

3.2.5 Tight-junction proteins and aquaporins

Tight junction complexes, composed of claudins and occludins, govern paracellular solute and water movements across teleost epithelia (Chasiotis et al., 2012; Sundell and Sundh, 2012; Tipsmark et al., 2008a, 2008b). In support of solute-linked water uptake, intestinal paracellular ionic permeability decreases during SW acclimation (Grosell, 2006; Sundell et al., 2003; Sundell and Sundh, 2012). The elevated expression of *claudin-3*, *-15*, and *-25b* in pufferfish (*Tetraodon nigroviridis*), European bass (*Dicentrarchus labrax*), and Atlantic salmon (*Salmo salar*) intestine during SW acclimation supports the involvement of their encoded proteins in regulating paracellular permeability (Bagherie-Lachidan et al., 2008; Boutet et al., 2006; Clelland et al., 2010; Tipsmark et al., 2010b; Tipsmark and Madsen, 2012). In general, there is limited information on the role of Prl in regulating intestinal claudins in vertebrates. In mice, Prl down regulated *claudin-3* expression in crypt cells (Teerapornpuntakit et al., 2012). In the only report that directly assessed Prl-claudin connections in fish intestine, Prl inhibited *claudin-15* and *-25b* gene expression in Atlantic salmon (Tipsmark et al., 2010b). This was notable given that *claudin-15* and *-25b* were enhanced during smoltification and SW acclimation (Tipsmark et al., 2010b). In contrast to *claudin-15* and *-25b*, *claudin-3a* and *-3b* were enhanced in FW-acclimated pufferfish; however, a link to Prl-signaling has not been assessed (Bagherie-Lachidan et al., 2008). While occludin was localized to the intestine of stenohaline (FW) goldfish (Chasiotis and Kelly, 2008), there is currently no information on intestinal occludin expression patterns in euryhaline fishes undergoing salinity acclimation or following hormone treatment.

Aqps are integral membrane proteins that facilitate passive movements of water and small non-ionic compounds across cell membranes (Cerdà and Finn, 2010). Teleosts coordinate the expression of Aqps in the intestine during SW acclimation as a

means to enhance transcellular osmotic permeability (Madsen et al., 2015; Sundell and Sundh, 2012). Accordingly, the expression of particular Aqps/*aqps* isoforms (e.g., Aqp1, -8, -10, -12) were enhanced in a series of teleosts during SW acclimation (Aoki et al., 2003; Deane et al., 2011; Engelund et al., 2013; Giffard-Mena et al., 2007; Jung et al., 2015; Kim et al., 2010; Lignot et al., 2002; Madsen et al., 2011, 2014; Martinez et al., 2005; Raldúa et al., 2008; Tipsmark et al., 2010c). To date, Prl-Aqp3 connections have only been characterized in branchial epithelium (Breves et al., 2016; Ellis et al., 2019). Future investigations should evaluate a role for Prl in inhibiting intestinal Aqps during FW acclimation; such an effect would complement the modulation of HCO_3^- secretion (Ferlazzo et al., 2012) that attenuates fluid absorption during FW acclimation.

3.2.6 Ca^{2+} absorption

Teleosts inhabiting FW must actively absorb Ca^{2+} across branchial and intestinal epithelia to counter diffusive loss to the external environment (Flik, 1993; Pang, 1973; Wongdee and Charoenphandhu, 2013). Greater than 90% of whole-body Ca^{2+} uptake is achieved via branchial (or epidermal) ionocytes (Flik et al., 1995; Lin and Hwang, 2016). Nonetheless, given that rates of intestinal Ca^{2+} uptake are greater when fish are acclimated to FW versus SW, the gut also seemingly supports Ca^{2+} homeostasis (Flik et al., 1996). The transcellular uptake of Ca^{2+} by ionocytes entails the entry of Ca^{2+} through an apical Ca^{2+} channel (ECaC; Trpv5/6) followed by basolateral exit via Ca^{2+}-ATPase (PMCA) and Na^+/Ca^{2+} exchanger (NCX) (Flik et al., 1995; Lin and Hwang, 2016). Prl operates as a hypercalcemic factor in multiple teleosts (Chakraborti and Mukherjee, 1995; Fargher and McKeown, 1989; Flik et al., 1989, 1994; Kaneko and Hirano, 1993; Pang et al., 1978; Wongdee and Charoenphandhu, 2013), at least in part, by stimulating branchial PMCA activity (Flik et al., 1996). In contrast to ionocytes, the basolateral transport of Ca^{2+} by enterocytes relies primarily on NCX rather than PMCA (Flik et al., 1993); thus, a role for Prl in the control of intestinal NCX expression/localization warrants investigation. Indeed, Prl enhanced intestinal Ca^{2+} absorption in mammals by stimulating the duodenal expression of *trpv6*, *pmca$_{1b}$*, and *ncx1* (Charoenphandhu et al., 2009; Wongdee et al., 2016). Given the conserved pathways for transcellular Ca^{2+} transport by mammals and teleosts (Lin and Hwang, 2016), and the hypercalcemic effects of Prl in both groups, it will be interesting to learn the extent to which connections between Prl and intestinal pathways for Ca^{2+} absorption are conserved.

4. Concluding remarks

When considering the collective actions of Prl within the gastrointestinal tract of teleosts, it becomes apparent that Prl has the capacity to both promote phenotypes supportive of FW acclimation and to inhibit phenotypes associated with SW acclimation (Fig. 1). To this point, this review has focused entirely on the activities of Prl in teleosts because to our knowledge no studies have identified distinct actions of Prl within the gastrointestinal tracts of jawless or cartilaginous fishes. Gh/Prl-family hormones are class-I helical cytokines (Huising et al., 2006). Ocampo Daza and Larhammar (2018) proposed that distinct Prl- and Gh-encoding genes arose in a vertebrate ancestor that preceded Agnathans. While only Gh has been identified in sea lamprey (*Petromyzon marinus*) (Kawauchi et al., 2002), seemingly due to loss of the *prl* gene (Ocampo Daza and Larhammar, 2018), sea lamprey were recently shown to express distinct *prlr* and *ghr* genes in the intestine (Gong et al., 2020). Thus, Prlr-mediated signaling emerged earlier in the vertebrate lineage than previously supposed and may participate in regulating osmoregulatory processes within basal vertebrates (albeit with Gh acting as a possible ligand). Barany et al. (2020) recently described regional specialization within sea lamprey intestine for solute and fluid transport that parallels patterns in teleosts. The next challenge is to link Gh/Prl-family hormone receptors in lamprey with specific intestinal processes. Perhaps the emergence of distinct *prlr* and *ghr* genes facilitated the evolution of complex control over intestinal processes; this control enabled migration between FW and marine habitats. Investigations of this nature will reveal how the regulatory roles of Gh/Prl-family hormones evolved to support the gastrointestinal processes that underlie hydromineral balance in fishes.

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CRediT authorship contribution statement

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Figure legend

Figure 1. Overview of the molecular, cellular, and organ level responses to prolactin (Prl) signaling in the gastrointestinal tract of teleosts. Processes stimulated by Prl are listed within green-shaded boxes with solid lines; processes inhibited by Prl are listed within red-shaded boxes with dashed lines. The demonstrated effects of Prl are listed alongside their associated study species (indicated within parentheses). Specific references: [1]Takahashi et al., 2007, [2]Takahashi et al., 2013, [3]Utida et al., 1972, [4]Morley et al., 1981, [5]Ferlazzo et al., 2012, [6]Tipsmark et al., 2010b, [7]Takahashi et al., 2006a, [8]Seale et al., 2014, [9]Kelly et al., 1999, [10]Peter et al., 2014, [11]Mainoya et al., 1982, [12]Madsen et al., 1997.

Highlights: ► Prl regulates gastrointestinal processes supportive of hydromineral balance. ► Prl receptors are expressed in esophagus and intestine of fishes. ► Prl directs the expression of intestinal solute transporters in euryhaline teleosts. ► Agnathans will provide insight into how Gh/Prl-family hormone function evolved.

Fig. 1