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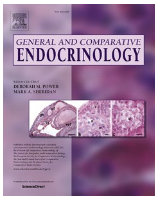

Minireview

Endocrine and osmoregulatory responses to tidally-changing salinities in fishes

Andre P. Seale [a,*], Jason P. Breves [b]

[a] *Department of Human Nutrition, Food and Animal Sciences, University of Hawaiʻi at Mānoa, 1955 East-West Road, Honolulu, HI 96822, USA*
[b] *Department of Biology, Skidmore College, 815 N. Broadway, Saratoga Springs, NY 12866, USA*

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ABSTRACT

Salinity is one of the main physical properties that govern the distribution of fishes across aquatic habitats. In order to maintain their body fluids near osmotic set points in the face of salinity changes, euryhaline fishes rely upon tissue-level osmotically-induced responses and systemic endocrine signaling to direct adaptive ion-transport processes in the gill and other critical osmoregulatory organs. Some euryhaline teleosts inhabit tidally influenced waters such as estuaries where salinity can vary between fresh water (FW) and seawater (SW). The physiological adaptations that underlie euryhalinity in teleosts have been traditionally identified in fish held under steady-state conditions or following unidirectional transfers between FW and SW. Far fewer studies have employed salinity regimes that simulate the tidal cycles that some euryhaline fishes may experience in their native habitats. With an emphasis on prolactin (Prl) signaling and branchial ionocytes, this mini-review contrasts the physiological responses between euryhaline fish responding to tidal versus unidirectional changes in salinity. Three patterns that emerged from studying Mozambique tilapia (*Oreochromis mossambicus*) subjected to tidally-changing salinities include, 1) fish can compensate for continuous and marked changes in external salinity to maintain osmoregulatory parameters within narrow ranges, 2) tilapia maintain branchial ionocyte populations in a fashion similar to SW-acclimated fish, and 3) there is a shift from systemic to local modulation of Prl signaling.

1. Introduction

Fishes are found across a wide range of aquatic environments where physical and chemical conditions shape their distribution and life history strategies. For instance, fish are distributed across environments with salinities ranging from freshwater (FW) (e.g., rivers, lakes, and marshes) to seawater (SW) (e.g., coastal waterways, bays, and the pelagic ocean). Further, fishes may inhabit extreme salinity environments such as hypersaline ponds and estuaries that undergo large tidal variations (Brauner et al., 2013). Canonically, euryhaline fish inhabit environments subject to wide salinity changes, though the extent of their tolerance to these changes is variable and largely dependent on the native environment and life history of the animal. Physiologically, euryhaline fishes (<10% of teleosts) can tolerate salinities ranging from FW (≤0.5 ppt) to SW (30–40 ppt) through their capacity to maintain salt and water balance (Brill et al., 2001; Evans and Claiborne, 2008; Schultz and McCormick, 2013). When residing in FW, fish produce large volumes of dilute urine while actively absorbing environmental ions to counterbalance their loss by diffusion. Alternatively, marine/SW-acclimated fish drink to replace (via solute-linked water absorption in the gut) the water that is lost by osmosis and actively extrude excess ions (Evans et al., 2005). The maintenance of hydromineral balance is largely achieved through the major osmoregulatory organs, namely the gill, intestine, and kidney, which respond to osmosensory and endocrine stimuli. The myriad adaptive responses that fishes from various clades exhibit in response to changes in environmental salinity have been thoroughly reviewed (Fiol and Kültz, 2007; Gonzalez, 2012; Marshall, 2012; McCormick and Bradshaw, 2006; Sakamoto and McCormick, 2006; Schulte, 2014). Studies which utilized euryhaline models to improve the collective understanding of how fish acclimate to environmental salinity have traditionally described the physiological states of animals acclimated to two or more steady-state salinities, or subjected to one way-transfers. There is no question these general paradigms will continue to provide the framework for understanding the physiological mechanisms that underlie environmental adaptation. Nonetheless, a need for employing experimental designs that address the highly-dynamic nature of particular aquatic environments has emerged in order to better understand the impacts of climate change and

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* Corresponding author.
E-mail address: seale@hawaii.edu (A.P. Seale).

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urbanization (Blewett et al., 2022). In turn, this mini-review focuses on findings that resulted from the use of experimental paradigms where physiological responses were described in fish subjected to tidally-changing salinity regimes that simulate the periodicity of salinity fluctuations in their native environments.

2. The influence of salinity acclimation history

Very few euryhaline fishes have been studied under tidally-changing salinity regimes. To our knowledge, studies investigating the physiological responses of euryhaline fish under a simulated tidal regime have been limited to the mummichog (*Fundulus heteroclitus*) and the Mozambique tilapia (*Oreochromis mossambicus*), which are known to withstand marked and frequent changes in salinity. Mummichogs are native to shallow coastal waters including estuaries and salt marshes of the western Atlantic Ocean between the Gulf of St. Lawrence and northeastern Florida (Robins et al., 1986). The Mozambique tilapia is native to estuaries and the lower reaches (within a mile from the tidal ebb and flow) of rivers from the Zambezi River to the southeast coast of South Africa (Trewavas, 1983). Thus, in certain locations, it is probable that both species are continuously exposed to changing salinities. In part because many acclimation studies have focused on the physiological responses following one-way transfers between salinities, a lingering question remains: to what extent do fish actually undergo physiological transformations/reversals when exposed to salinity challenges in periodic fashions? One approach to address this question is to consider whether a fish that experiences a ‘one-time’ change in salinity from FW to SW, or vice-versa, responds in a similar manner as an individual previously, and periodically, exposed to both salinities. Survival, the ultimate indication of acclimation success, provides a clue to understanding the effects that acclimation history imparts on future salinity challenges.

In euryhaline Japanese medaka (*Oryzias latipes*), pre-adaptation to elevated salinity facilitated subsequent acclimation to SW (Miyanishi et al., 2016). FW-acclimated fish were first pre-acclimated to 50% SW and then returned to FW. Twenty-five percent of the fish that had been pre-acclimated to 50% SW survived a direct transfer from FW to SW, while fish that were not previously exposed to 50% SW did not survive transfer to SW. Likewise, Mozambique tilapia, which can eventually be acclimated to salinities far exceeding those of SW (Uchida et al., 2000), fail to survive a direct transfer from FW to SW unless they are transitioned over an extended period, pre-acclimated to an intermediate salinity, or pre-exposed to a regime of changing salinities (Inokuchi et al., 2021; Moorman et al., 2015; Seale et al., 2002). The congeneric Nile tilapia (*O. niloticus*) is less tolerant of elevations in salinity, as evidenced by its inability to survive direct transfer from FW to brackish water (BW; 20 ppt) for more than 24 h (Yamaguchi et al., 2018). The more narrow salinity tolerance of Nile tilapia is reflected by a sharp and uncontrolled rise in plasma osmolality following transfer from FW to BW (Yamaguchi et al., 2018). Plasma osmolality, a measure of the amount of solutes per kg of solution, largely reflects the concentrations of Na^+ and Cl^-, which are also the principal ionic constituents of environmental water and are actively regulated through epithelial cells for maintaining organismal salt and water balance. It stands unresolved whether the ability of *O. niloticus* to tolerate BW/SW conditions can be improved with pre-exposure to sublethal periodic changes in salinity.

3. Osmotic homeostasis in tidally-changing salinities

Studies with the mummichog on the effects of acute salinity transfers on transepithelial potential (TEP) indicated the prevalence of Na^+ diffusion in SW-acclimated fish and a limitation of Na^+ loss in FW-acclimated fish (Wood and Grosell, 2008). Interestingly, when fish were tested under conditions simulating a tidal cycle their TEP was distinct from fish acclimated to FW and more closely resembled fish acclimated to SW (Wood and Grosell, 2009). Nonetheless, when mummichogs transiently move into lower salinities they can do so without large disruptions in osmotic homeostasis (Wood and Grosell, 2009). By tracking ion fluxes in response to salinity changes, these studies also provided insight into how transient shifts in salinity can be tolerated with the least metabolic cost and with minimal impact on the configuration of physiological processes required for osmotic homeostasis.

As observed in mummichogs, Mozambique tilapia can also maintain osmotic homeostasis under tidally-changing salinities. Despite the wide range of salinities in which the Mozambique tilapia is found, it regulates plasma osmolality within a narrow range, typically around 320 mOsm/kg in FW-acclimated fish and 335 mOsm/kg in SW-acclimated fish (Seale et al., 2006a; Seale et al., 2002; Yada et al., 1994). However, following a one-way transfer from SW to FW, plasma osmolality may briefly reach as low as 280 mOsm/kg, while after a change from FW to 80% SW, it may climb to over 400 mOsm/kg for a short period (Breves et al., 2011; Seale et al., 2006a; Seale et al., 2012a; Seale et al., 2002; Yada et al., 1994). Most previous work investigating the links between salinity tolerance and key physiological processes such as osmoregulation and growth in Mozambique tilapia has focused on fish reared under steady-state salinity conditions (FW or SW) or transferred from FW to SW and vice-versa (Borski et al., 1994; Breves et al., 2010a; Riley et al., 2003; Seale et al., 2006a; Seale et al., 2002). In Mozambique tilapia, a tidal regime (TR) paradigm was first tested in fish that were continuously reared in salinities alternating between FW and SW every 6 h from the early fry stages until 4 months of age (Fig. 1A) (Moorman et al., 2014). A tidally-changing environment was simulated by maintaining fish in aquaria supplied with water from reservoirs containing FW or SW equipped with submersible pumps hooked to automatic timers offset by 6 h (Fig. 1B). Studies employing the TR paradigm allowed for a comparison between the FW- and SW-phases of the tidal cycle (TF and TS, respectively) relative to comparisons between FW and SW steady-state regimes (Fig. 1A). In contrast to the wide excursions in plasma osmolality typically observed by 6 h after a ‘one-time’ transfer from FW to SW, tilapia reared under a TR showed a minor elevation of plasma osmolality in TS (Fig. 2) (Moorman et al., 2014; Moorman et al., 2015; Pavlosky et al., 2019; Seale et al., 2019). In fact, changes in osmolality were within the range found in fish maintained in steady-state FW or SW (Fig. 2). The capacity to prevent wide shifts in plasma osmolality under a TR suggests that tidal fish are particularly effective in maintaining osmoregulatory homeostasis.

The pathways that connect changes in environmental salinity with adaptive physiological responses involve signaling mechanisms that couple the perception of osmotic stimuli with the molecular and cellular processes central to the maintenance of osmotic balance. These signaling mechanisms, which involve direct osmosensing, osmoreceptors, and the endocrine control of ion and water transport within osmoregulatory epithelia, have been thoroughly reviewed (Breves et al., 2014; Fiol and Kültz, 2007; Guh et al., 2015; Marshall, 2012; McCormick and Bradshaw, 2006; Seale et al., 2005, 2006b; Seale et al., 2020a; Seale et al., 2012b) and synthetized into a framework that integrates multiple sensory and effector elements (Evans and Kültz, 2020; Kültz, 2012). Here, these signaling mechanisms are discussed within the context of animals reared under tidal paradigms.

4. Hormonal responses to tidally-changing salinities

In response to an osmotic challenge, euryhaline species integrate osmosensing, systemic and local endocrine signaling, and effector mechanisms. Aspects of these distinct, yet interacting, processes are summarized in Fig. 3 and compared between Mozambique tilapia acclimated to steady-state salinities (FW and SW) and TR (TF and TS). At the organismal level, tidal changes in environmental salinity (Fig. 3A) elicited narrow oscillations in plasma osmolality, between about 320 and 345 mOsm/kg (Fig. 3B). At the level of the pituitary, systemic osmoreception in Mozambique tilapia occurs at least partially through

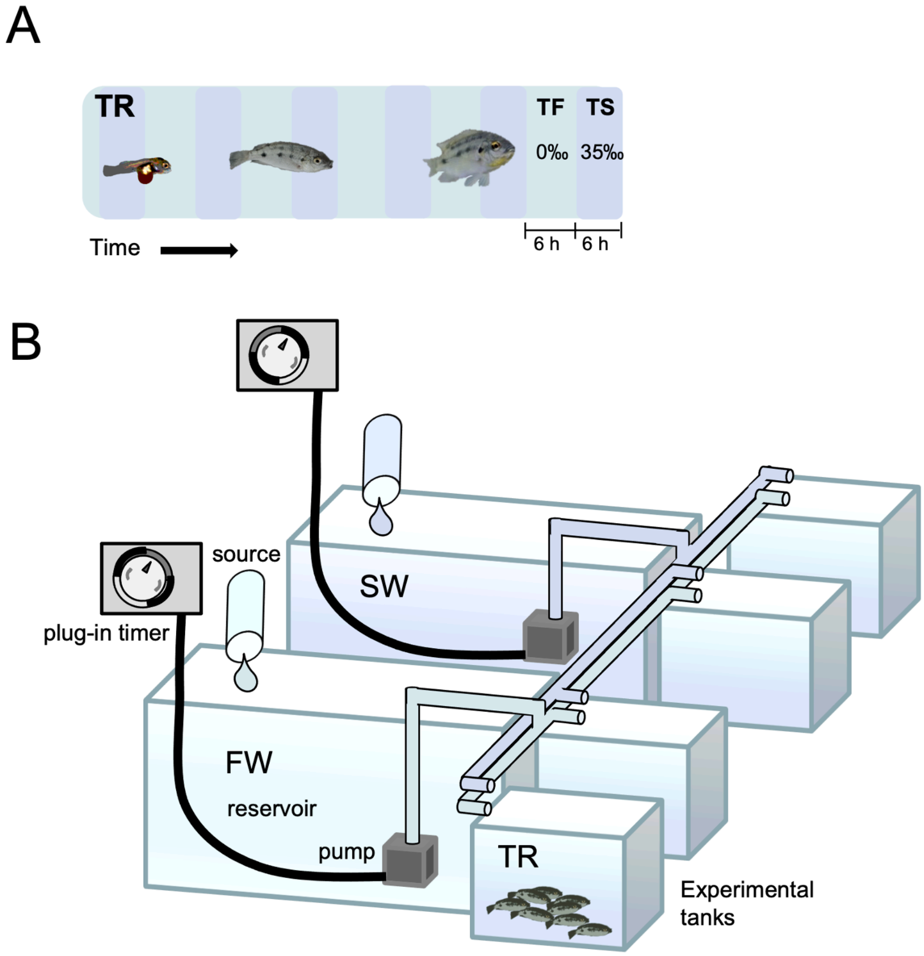

Fig. 1. Experimental tidal regime (TR) paradigm with fish reared in alternating FW and SW phases (TF and TS, respectively); blue bands represent SW and light blue bands represent FW (A). Illustration of the tank setup employed for TR experimental paradigms (B). The setup is designed to supply FW or SW to experimental tanks every 6 h, thereby simulating a tidal cycle. Reservoir tanks containing either FW or SW supply water to experimental tanks via a submersible pump. The pump is plugged into a timer that is offset by 6 h between the FW and SW reservoirs.

prolactin (Prl), a pleiotropic hormone that is both highly osmosensitive and effective at directing hyperosmoregulatory processes (Grau and Helms, 1989; Seale et al., 2006b; Seale et al., 2012b). In Mozambique tilapia, the release of two Prl isoforms, Prl_{177} and Prl_{188}, increased in response to falls in extracellular osmolality *in vitro* or following an *in vivo* transfer from SW to FW (Grau et al., 1981; Nicoll et al., 1981; Seale et al., 2012a; Seale et al., 2002; Yada et al., 1994). One notable exception to the general pattern of an inverse relationship between plasma Prl and extracellular osmolality was observed in fish reared in a TR. The gene expression and release of both Prls became decoupled from extracellular osmolality; circulating Prl levels resembled those found in SW-acclimated fish (Fig. 3C and D) (Moorman et al., 2014; Moorman et al., 2015; Seale et al., 2019). These findings suggest that Prl release is less sensitive to ambient osmolality under a TR. However, if extracellular osmolality abruptly breaks below 320 mOsm/kg, plasma Prl levels will rise (Seale et al., 2019). Accordingly, Prl increased only after fish previously maintained under a TR had been transferred to FW for 24 h. This pattern of circulating Prl paralleled *prl* gene expression in the pituitary (Moorman et al., 2015). Collectively, these observations indicate that a point exists between 6 and 24 h after FW-exposure when elevated plasma Prl becomes necessary to maintain osmotic balance.

Teleost Prls exert their actions by interacting with transmembrane receptors, two of which, Prl receptor 1 (Prlr1) and -2 (Prlr2), have been identified in tilapia (Fiol et al., 2009). Branchial gene expression of *prlr1* and *-2* responds to both osmotic stimuli and circulating Prl. While branchial *prlr1* was stimulated by Prl_{177} and Prl_{188} yet unresponsive to extracellular osmolality, *prlr2* was unresponsive to both Prls and upregulated following an increase in osmolality (Inokuchi et al., 2015). In pituitary Prl cells, the expression patterns of both *prlrs* in relation to extracellular osmolality were similar to those observed in the gill, indicating that in addition to mediating Prl signaling in target tissues (Seale et al., 2012a), Prlrs also mediate osmotically-modulated autocrine responses in the pituitary (Yamaguchi et al., 2016). In contrast to the modest changes in the levels of *prl* transcripts and plasma Prls seen under a TR, the gene expression of branchial *prlrs* changed during each phase of the tidal cycle. For instance, *prlr1* increased in TF and decreased in TS (Fig. 3E) (Moorman et al., 2014; Moorman et al., 2015; Seale et al., 2019). By contrast, *prlr2* responded in the opposite direction by increasing in TS and decreasing in TF. These observations led us to propose that under tidal conditions the endocrine control of osmoregulatory processes shifts from the systemic regulation of hormone secretion to the local modulation of hormonal action via changes in receptor expression (Seale et al., 2019).

Changes in salinity affect the release of other pleiotropic pituitary hormones such as growth hormone (Gh). Unlike Prl, however, Gh increased in response to elevations in salinity, *in vivo* (Helms et al., 1987; McCormick, 2001; Pierce et al., 2007; Sakamoto and Hirano, 1993; Sakamoto et al., 1997), and extracellular osmolality, *in vitro* (Borski et al., 1994; Seale et al., 2006a; Seale et al., 2002). These responses are consistent with the higher growth rates observed in tilapia reared in SW versus lower salinities (Kuwaye et al., 1993; Morgan and Iwama, 1991; Riley et al., 2002; Ron et al., 1995; Shepherd et al., 1997; Sparks et al., 2003). Moreover, Gh is also tied to branchial processes that support SW-acclimation (McCormick and Bradshaw, 2006). The actions of Gh on osmoregulatory systems is mediated, at least partially, by increased plasma insulin-like growth factor 1 (Igf1) levels (Mancera and McCormick, 1998; Sakamoto and McCormick, 2006; Seidelin and Madsen, 1999; Tipsmark et al., 2007) and is associated with the enhanced

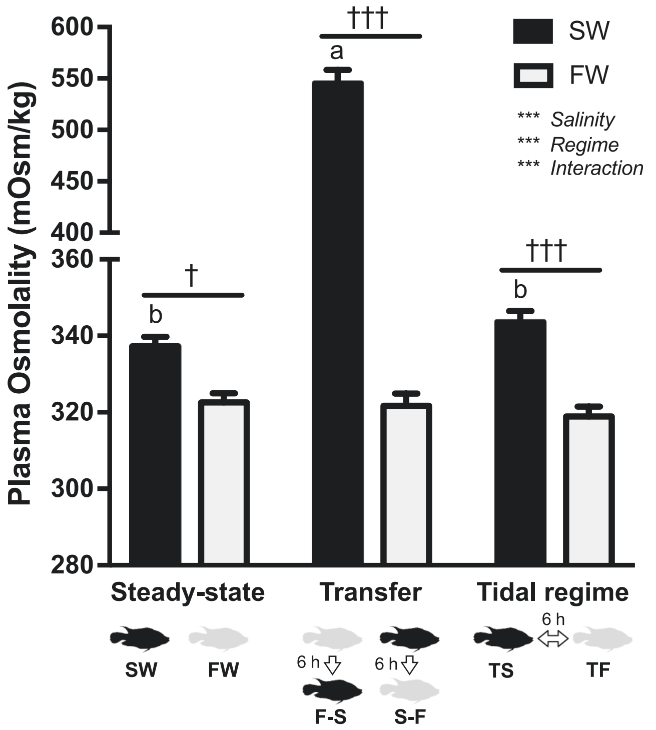

Fig. 2. Plasma osmolalities of Mozambique tilapia: 1) in steady-state seawater (SW) and fresh water (FW); 2) transferred one-way from FW to SW (F-S) and from SW to FW (S-F); and 3) in a tidal regime sampled in the SW phase (TS) and in the FW phase (TF). Transferred fish were sampled at 6 h. Bars represent mean ± S.E.M. Plasma osmolality of fish in SW (black) and FW (grey) ($n = 10$–20). A complete transition between salinities in the transfer and tidal regime groups occurred within 1 h. Data were analyzed by 2-way ANOVA with acclimation regime and salinity as main effects, followed by Bonferroni's post-hoc test. *** indicate main and interaction effects at $P < 0.001$; †, ††† indicate significant differences between salinities at each acclimation regime at $P < 0.05$ and $P < 0.01$, respectively. Letters not shared between bars indicate significant differences between acclimation regimes within salinities at $P < 0.05$. Figure adapted from Moorman et al. (2015)

expression of branchial ion pumps and transporters (Pelis and McCormick, 2001; Tipsmark and Madsen, 2009).

Rearing Mozambique tilapia under a TR increased pituitary *gh* expression and plasma Gh to levels above those of both steady-state SW- and FW-acclimated fish; however, there were no differences detected between the two phases of the TR (Fig. 3C and D) (Moorman et al., 2016). The elevations in pituitary *gh* and plasma Gh observed in tilapia reared in a TR are consistent with the sexually dimorphic regulation of growth and the higher growth rates, in both sexes, of fish reared in TR versus steady-state FW or SW (Moorman et al., 2016; Seale et al., 2020b). The transcriptional activation of downstream components of the Gh/Igf system in fish reared in TR, such as the growth hormone receptor (*ghr*), *igf1*, and *igf2* in liver and muscle, followed patterns resembling the *prlrs* where transcript levels changed between TF and TS (Fig. 3F and G) (Moorman et al., 2016). Specifically, the expression of *ghr* in liver and muscle, and *igfs* in liver, was higher in TF than in TS. These patterns suggest that Gh-sensitivity in muscle and liver is impacted by environmental salinity in an oscillatory fashion that may underlie the increased growth observed in fish reared under TR. Moreover, because the changes in *ghr* and *igfs* resembled the dynamic regulation of *prlrs* observed in the gill under an identical regime, they contribute to a broader pattern of endocrine regulation where relative systemic stability is coupled with organ-level changes at the level of receptors and downstream effectors in response to tidally-changing salinities.

5. Effectors of ion transport in tidally-changing salinities

Whether regulated by endocrine factors, or in direct response to changes in salinity, effectors of hydromineral balance respond uniquely to tidally-changing salinities. A closer look at the branchial 'ionocytes' (also termed 'mitochondria-rich cells') of tilapia illustrates this notion. In Mozambique tilapia, four ionocyte sub-types have been identified based upon the expression of ion-transporting proteins: Type-I cells express an apical renal outer medullary K^+ channel (Romka) and basolateral Na^+/K^+-ATPase (Nka; Atp1a); Type-II cells express an apical Na^+/Cl^- cotransporter 2 (Ncc2; Slc12a10) and basolateral Nka; Type-III cells are characterized by an apical Na^+/H^+ exchanger 3 (Nhe3; Slc9a3) in addition to basolateral Nka; Type-IV cells express an apical cystic fibrosis transmembrane conductance regulator (Cftr) and basolateral $Na^+/K^+/2Cl^-$ cotransporter 1a (Nkcc1a; Slc12a2a) and Nka (Hiroi et al., 2005; Kaneko et al., 2008; Furukawa et al., 2014).

The functional and morphological changes that occur among branchial ionocytes have been traditionally identified through one-way salinity transfer paradigms. By examining the ionocytes of tilapia maintained under a TR, we observed that ionocytes do not necessarily change in response to the FW- and SW-phases of a tidal cycle as would be expected if such changes mimicked those seen during one-way salinity transfers. For example, tilapia raised under a TR exhibited Cftr- and Nkcc-immunopositive cells that did not change between the FW- and SW-phases of the tidal cycle; immunoreactivity more closely approximated the patterns observed in fish continuously maintained in SW (Moorman et al., 2014). In addition, fish acclimated to the TR maintained the gene expression of pumps and transporters involved in ion uptake, such as *ncc2*, *nkaα1a*, and *nhe3* (Hiroi et al., 2008; Inokuchi et al., 2008; Tipsmark et al., 2011) at higher levels than fish acclimated to steady-state SW, but much lower than fish acclimated to FW. In some cases, such as with *ncc2*, there were differences between TF and TS, but they typically occurred within a much narrower range than observed between steady-state FW and SW fish (Fig. 3E) (Moorman et al., 2014). By contrast, the expression of genes encoding effectors of ion secretion, such as *nkcc1a* and *cftr*, fluctuated between TF and TS with the same magnitude observed between steady-state FW and SW acclimated fish (Fig. 3E). These patterns of ionocyte regulation in tilapia are consistent with the similarities observed in TEP measurements between mummichogs reared in SW versus tidally-changing environments (Wood and Grosell, 2009), though some important differences in the regulation of molecular transducers of ion and water transport are worth noting. While tilapia in TF and TS maintained ionocyte numbers similar to fish in SW, Cftr immunoreactivity was dramatically decreased in TF fish (Moorman et al., 2014). The decrease in Cftr abundance that was evident in TF is indicative of salinity-dependent trafficking of Cftr to the apical membrane (Marshall and Singer, 2002). This apparent regulation of Cftr expression is important because otherwise the extrusion of Cl^- by Type-IV ionocytes would be highly deleterious to fish in FW. Hence, the rapid decrease in Cftr contributes to how fish exposed to tidal conditions can survive in FW for 6 h without recruiting ion-absorptive ionocytes.

In addition to the changes in Cftr, branchial *aquaporin 3* (*aqp3*) expression differed between the two phases of the tidal cycle. This suggests that modulating Aqp3 function (possibly water/urea/glycerol permeability) is important even in fish that experience a different salinity for just 6 h (Moorman et al., 2014; Moorman et al., 2015). Although responding in opposing fashions, *cftr* and *aqp3* were highly sensitive to continually changing salinities, and especially in response to transfers from TR to steady-state salinities (Moorman et al., 2015). The high sensitivity of these transcripts to tidally-changing salinities is also consistent with the previously proposed roles of their encoded proteins in branchial mechanosensory signal transduction (Cutler and Cramb, 2002; Madsen et al., 2014; Marshall, 2003; Marshall, 2011; Marshall and Singer, 2002; Watanabe et al., 2005) and Prl cell osmoreception through osmotically-driven changes in cell volume (Seale et al., 2003; Seale et al., 2012b; Watanabe et al., 2009; Weber et al., 2004). Therefore, the

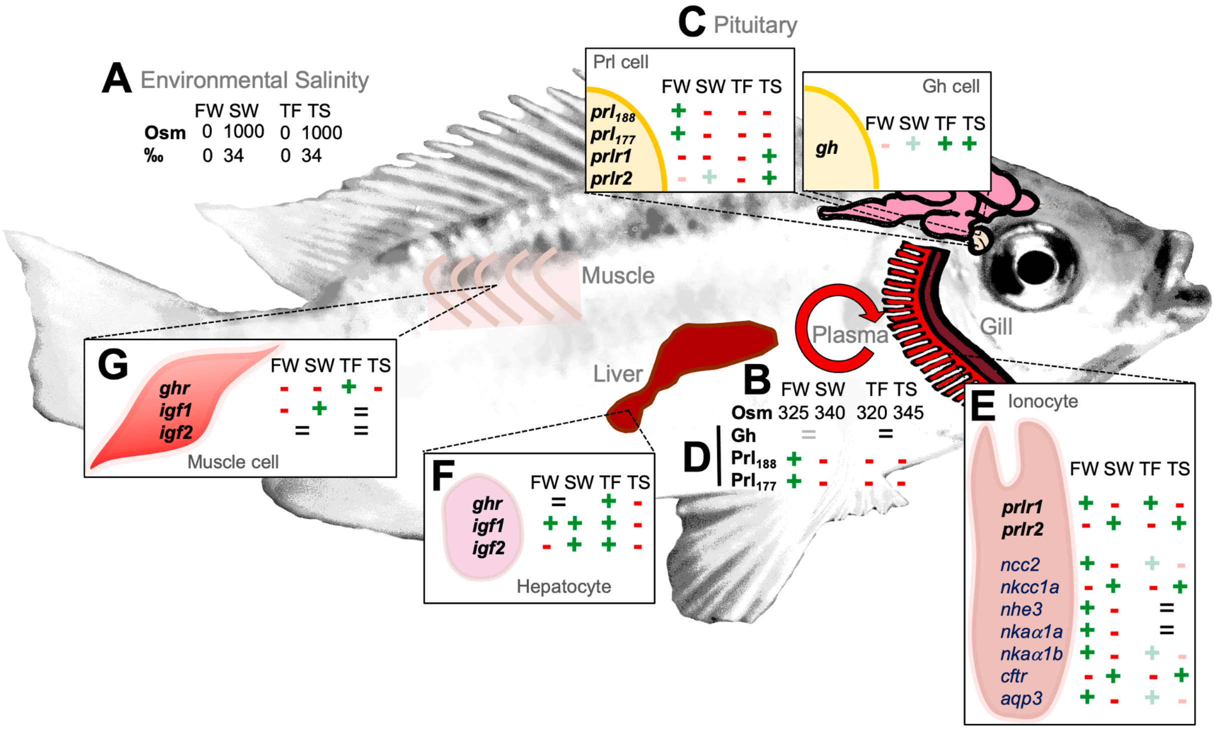

Fig. 3. Effects of salinity regime on endocrine regulators of growth and ionoregulation. Plus and minus signs next to each gene transcript indicate an increase or decrease, respectively, relative to each other; faded signs denote attenuated responses and equal signs denote similar values that are intermediate to the other values being compared. Environmental salinity ranges in steady-state FW and SW and tidally-changing salinities between FW (TF) and SW (TS) (A). Changes in salinity elicit changes in plasma osmolality within narrow ranges for fish in steady-state FW and SW, and TF and TS (B). prl_{177} and prl_{188} expression is higher in steady-state FW versus SW while no difference is observed between fish in TF and TS; the opposite pattern is seen with *prlr1*, which was unchanged between FW- and SW-acclimated fish and different between TF and TS; expression of *gh* is highest in TF and TS, followed by SW and FW (C). Plasma Prl_{188} and Prl_{177} levels follow a similar pattern as pituitary levels of their associated gene transcripts; Prl_{188} and Prl_{177} are elevated in steady-state FW relative to SW, but unchanged between TF and TS; plasma Gh levels are similar between all salinity regimes (D). Branchial *prlr1* was consistently elevated in FW and TF fish relative to SW and TS fish, respectively, while *prlr2*, *nkcc1a*, and *cftr* levels were elevated in fish in SW and TS relative to those in FW and TF; *ncc2*, *nka* α *1b*, and *aqp3* showed the same direction of response in TF and TS fish compared to FW and SW, but the magnitude of expression was attenuated and generally lower than that of steady-state fish. Lastly, *nhe3* and *nka* α *1a* were differentially expressed between FW and SW but not between TF and TS (E). In liver, *ghr* and *igf1* did not vary between steady-state salinities, but changed between TF and TS; *igf2* changed between steady-state salinities and between TF and TS (F). In muscle, *ghr* did not change between steady-state salinities but changed between TF and TS; transcript levels in FW and SW fish were low compared with those in TF. The expression of *igfs* was relatively unchanged across all salinity regimes, with the exception of the elevation of *igf1* in fish in SW relative to those in FW (G). This summary of plasma hormone and gene expression patterns in steady-state and tidal salinities is based on results from Moorman et al. (2014), Moorman et al. (2015), Moorman et al. (2016), Pavlosky et al. (2019), Seale et al. (2020b), and Seale et al. (2019). Abbreviations: Osm: osmolality (mOsm/kg); FW: fresh water; SW: seawater; TF: FW phase of tidal cycle; TS: SW phase of tidal cycle; prl_{188}: *prolactin 188*; prl_{177}: *prolactin 177*; *gh*: *growth hormone*; *ghr*: *growth hormone receptor*; *igf1* and −*2*: *insulin-like growth factor 1 and* −*2*; *prlr1* and −*2*: *prolactin receptor 1 and* −*2*; *ncc2*: *Na$^+$/Cl$^-$ cotransporter 2*; *nkcc1a*: *Na$^+$/K$^+$/2Cl$^-$ cotransporter 1a*; *nhe3*: *Na$^+$/H$^+$ exchanger 3*; *nka* α *1a* and -α*1b*: *Na$^+$/K$^+$-ATPase alpha 1a and -alpha 1b*; *cftr*: *cystic fibrosis transmembrane conductance regulator*; *aqp3*: *aquaporin 3*. Abbreviations in italics denote gene transcripts.

dynamic nature of Cftr and Aqp3 expression in TR further strengthens the notion that each one plays indispensable roles in maintaining hydromineral balance, where an abundance of the former in FW would underlie Cl$^-$ loss and an abundance of the latter in SW could lead to excessive osmotic water loss. In addition to the acute responses of *cftr* and *aqp3* to extracellular osmolality, evidence from studies employing the TR paradigm indicates that these and other osmoregulation-related transcripts may be tied to hormone receptor dynamics in TR (Seale et al., 2019). The expression of *ncc2* and *aqp3*, for example, is upregulated during FW acclimation and is stimulated by Prl (Breves et al., 2016; Breves et al., 2010b), whose actions in tidal conditions may be mainly modulated by receptor expression rather than circulating levels of hormone. Thus, the observed changes in *prlr* expression may represent a strategy to fine-tune the actions of Prl in circulation within time-frames that may be too short for pituitary-based processes to respond.

The functional consequences of tilapia experiencing tidal conditions has also been experimentally addressed through transfers from TR to steady-state environments (Moorman et al., 2015) and vice versa (Pavlosky et al., 2019). Notably, when compared with fish reared in FW, fish reared in a TR had a significantly improved ability to survive direct transfer to SW (Moorman et al., 2015). When adult fish (>2 years in age) were transferred from either steady-state FW or SW to TR, however, they were able to survive the abrupt and cyclical salinity changes imposed by the TR, and within seven days, exhibited ion-transporter/channel transcriptional patterns similar to those observed in fish reared in TR from the fry stage (Pavlosky et al., 2019). Thus, acclimation to a TR can occur within a range of life stages, where a combination of direct and endocrine-mediated responses to osmotic stimuli enable fish to cope with the vicissitudes of estuarine environments.

6. Conclusion and future perspectives

Studies employing simulations of tidally-changing salinities provide an important perspective on the adaptive processes that support salinity acclimation. Euryhaline teleosts, such as mummichogs and Mozambique tilapia, tolerant of environments characterized by frequent changes in salinity are ideally suited for such investigations. The rearing conditions/life history of a given individual is a key determinant of that individual's capacity to exhibit plastic osmoregulatory activities. In both species, extended pre-exposures to tidally-changing salinities enabled their performance in stable hypo- or hyperosmotic environments (Moorman et al., 2015; Wood and Grosell, 2009). Underlying this adaptive capacity are distinct patterns of endocrine control over downstream effectors of ion transport that enable plasma osmolality to remain within a narrow range. While more closely resembling fish acclimated to hyperosmotic environments, fish reared under a TR maintain a distinct osmoregulatory strategy that does not fully coincide with animals exposed to 'one-time' transfers between FW and SW.

There is no question that a broad collection of hormones beyond Prl and Gh play key roles in promoting hydromineral balance in teleosts (Takei et al., 2014). For instance, cortisol is 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). While cortisol exhibits clear responses to 'one-time' changes in salinity (Kajimura et al., 2004), to our knowledge, there is no information on the patterns of its release during tidally-changing conditions. It will be interesting to learn whether plasma cortisol levels change in parallel with environmental salinity, or like circulating Prl levels, become uncoupled from changes in plasma osmolality during tidal cycles.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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