Development of the hypothalamus-pituitary-interrenal axis

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Key points

- The hypothalamus-pituitary-interrenal (HPI) axis is a hormone cascade that regulates cortisol secretion and is activated in response to a stressful stimulus.
- The hypothalamus, pituitary, and interrenal cells are present in zebrafish embryos as early as 24 h post-fertilization and endogenous cortisol production is initiated around the time of hatching.
- A stress-induced increase in cortisol typically does not occur until sometime after hatching, consistent with a stress hyporesponsive period.
- Maternal deposition of stress-related genes and cortisol into oocytes may influence early developmental events, and this deposition is affected by maternal stress. These maternal effects influence offspring phenotype.

Glossary

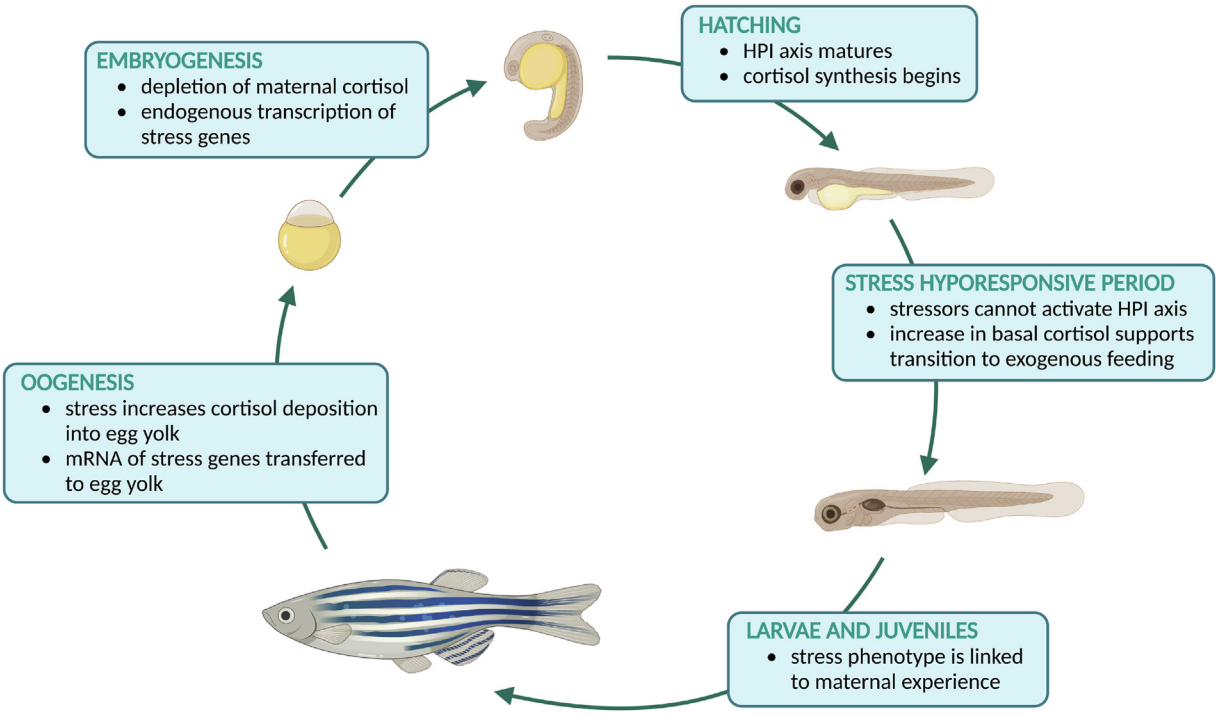
Adrenocorticotropic hormone (ACTH) A hormone produced in the anterior pituitary gland from the precursor proopiomelanocortin (pomc) that regulates cortisol synthesis.
Corticotropin-releasing factor (CRF) A neuropeptide hormone produced in and released from the preoptic area of the hypothalamus (and elsewhere); initiates the HPI axis.
Cortisol A steroid hormone. In teleosts, this hormone acts as both the principal glucocorticoid and mineralocorticoid.
Critical window A sensitive period of development during which environmental factors can induce phenotypic changes.
Glucocorticoid A generic term for a steroid hormone that regulates energy balance.
HPI axis The hypothalamus-pituitary-interrenal (HPI) axis regulates cortisol production and is activated in response to stress.
Mineralocorticoid A generic term for a steroid hormone that regulates ion and water balance.
Stress hyporesponsive period The time between the onset of endogenous cortisol production and when a stressor can activate the HPI axis.
Stressor An actual or perceived stimulus that disrupts homeostasis.

Abstract

The development and maturation of the hypothalamus-pituitary-interrenal axis (HPI axis) determines when a fish will be able to respond to environmental stressors through active and integrative homeostatic regulation. Studies from zebrafish provide a comprehensive overview of HPI axis development. Key genes are expressed within HPI axis structures shortly after they are formed, and endogenous cortisol synthesis begins around hatching and increases as the fish prepares for exogenous feeding. Activation of the HPI axis in response to a stressor is delayed relative to the onset of endogenous cortisol synthesis, supporting a stress hyporesponsive period that may help protect fish larvae during a critical window of development. At the same time, many players in the HPI axis, including corticotropin-releasing factor and cortisol, can

modulate embryo phenotypes even before the HPI axis has fully formed and matured. The fact that many of these same components are transferred from female fish into egg yolk suggests a mechanism for transgenerational environment-phenotype matching in the context of stress.

Teaching slide



Introduction

The need for a fish to respond to stress is as inevitable as it is essential. When faced with a stressor, fish—like all vertebrates—mount a coordinated physiological response that aids in overcoming the challenge and recovering homeostasis. A key player in these events is the steroid hormone cortisol, which is produced by specialized cells in the kidney known as interrenal cells. Cortisol synthesis and secretion are regulated by the hypothalamus-pituitary-interrenal (HPI) axis, a hormone cascade initiated by corticotropin-releasing factor (CRF) release from the hypothalamus. CRF stimulates adrenocorticotropic hormone (ACTH) release from the adenohypophysis into the circulation, which then stimulates the synthesis and secretion of cortisol. Activation of the HPI axis and the subsequent increase in circulating cortisol is a tell-tale response to stress that, among its many functions, drives the catabolism of energy reserves to support the increased energetic demands of stress and recovery. However, the range of cortisol-mediated events is plentiful given the near ubiquitous distribution of intracellular cortisol receptors (i.e., glucocorticoid and mineralocorticoid receptors, GR and MR) and the broad influence of these receptor-ligand complexes on gene expression.

In early life stages, cortisol-induced changes in gene expression during critical developmental windows can impart lasting phenotypic effects. For example, using zebrafish, several studies have shown that experimental manipulation of cortisol signaling during ontogeny impairs the development of major organ systems, including the nervous and musculoskeletal systems (Faught and Vijayan, 2019; Nesan et al., 2012; Nesan and Vijayan, 2012, 2016; Pikulkaew et al., 2011; Wilson et al., 2013), which may ultimately impact survival. Moreover, there is growing evidence that stressors experienced at early life stages can impart behavioral effects in fish, which persist into later life stages (Ivy et al., 2017; Reyes-Contreras and Taborsky, 2022). Therefore, understanding how and when fish gain the capacity to activate the HPI axis and increase cortisol levels in response to stressors can help us predict the impacts of anthropogenic stressors on fish populations, implement better fish husbandry practices, and achieve success in conservation initiatives (Bernier and Alderman, 2022).

This article summarizes the normal ontogeny of the HPI axis in teleost fish, including its morphological and molecular components, their integration into a responsive hormone cascade, and the role of maternal experience in shaping this process. Here, an emphasis on the widely used experimental model species, zebrafish (*Danio rerio*), provides the most comprehensive and integrated account of these early life events. Still, studies from other fish species are included where possible.

Morphological and molecular development

Since the early 1990s, the zebrafish has served as a keystone comparative model in developmental biology. Of relevance here, the transparent embryos, rapid rate of development (fertilization to hatch is ~55 h post-fertilization, hpf), and wealth of available molecular tools have enabled stress biology researchers to build a deep and comprehensive understanding of how the HPI axis forms and matures. An overview of hypothalamus, pituitary, and interrenal cell morphogenesis, as well as the onset of gene expression related to HPI axis function, provide a detailed ontogenic timeline of HPI axis ontogeny in zebrafish. Detailed reviews are available for curious readers (Bacila et al., 2021; Nesan and Vijayan, 2013).

Hypothalamus

The hypothalamus is the most ventral region of the diencephalon. Using a variety of cell fate mapping approaches, it is possible to trace the origin of hypothalamic neurons to discrete cell populations within the anterior neuroectoderm of zebrafish gastrulae and track their movement from the neural plate during somitogenesis (Russek-Blum et al., 2009). The dopaminergic neurons of the hypothalamus that will exert trophic control over the anterior pituitary are first detected at 18 hpf (Machluf et al., 2011), and *crf* expression is localized in this region by 28 hpf (Chandrasekar et al., 2007). By 48 hpf, just prior to hatching, *crf*-expressing neurons are visible as bilaterally paired cell clusters in what is now the preoptic region of the hypothalamus (**Fig. 1**A), as well as elsewhere in the brain, and *crf* transcription increases exponentially after hatch (Alderman and Bernier, 2009).

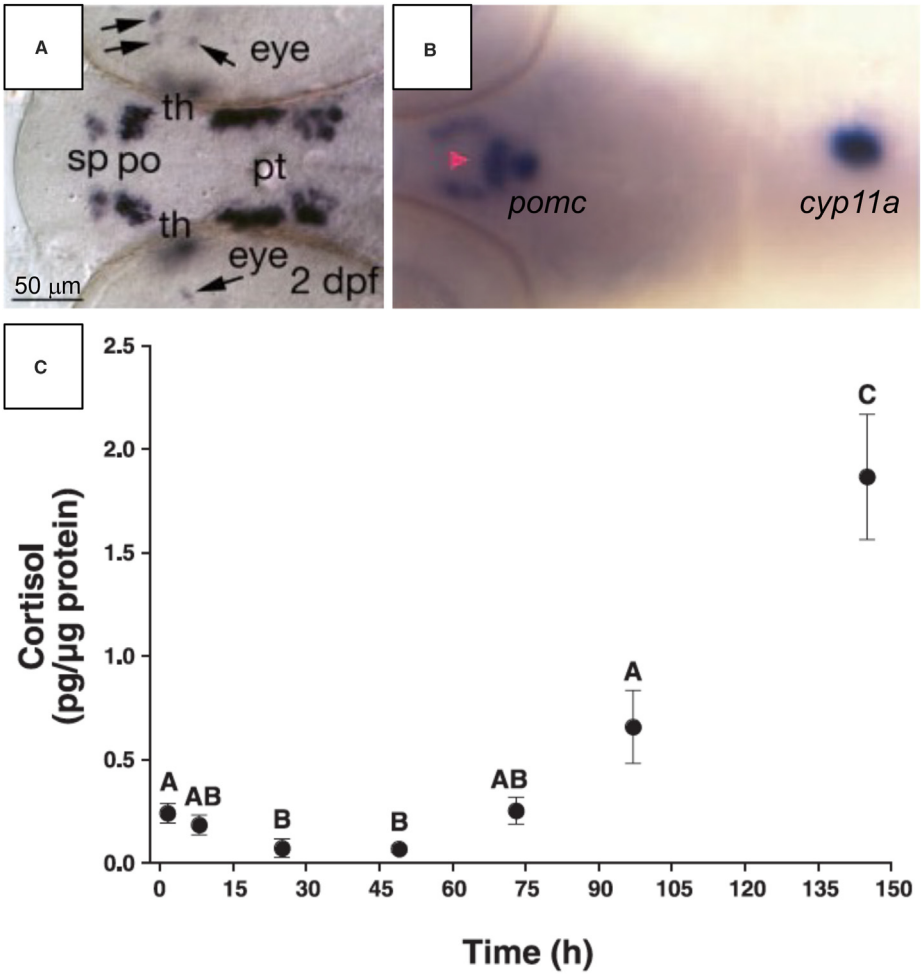


Fig. 1 Evidence for HPI axis maturation in zebrafish using *in situ hybridization* to localize the expression of specific genes in the developing embryo and hormone quantification to track baseline cortisol levels in whole embryos and larvae. (A) Expression of *corticotropin-releasing factor* (*crf*) is localized in the preoptic region (po) of the hypothalamus as well as other brain regions (pt, posterior tuberculum; sp, subpallium; th, thalamus) and in the eyes (arrows) at 2 days post fertilization (dpf). (B) Expression of *proopiomelanocortin* (*pomc*, a precursor of adrenocorticotropic hormone, ACTH) is visible in the pituitary of a 2 dpf embryo (red arrowhead), and several steroidogenic enzymes, including *cytochrome P450 side-chain cleavage* (*cyp11a*), are expressed by the kidney interrenal cells. (C) Cortisol levels during the first 6 dpf demonstrate a depletion of maternally-deposited cortisol during embryogenesis and a subsequent increase in cortisol after hatching as endogenous synthesis capacity increases. Images are from (A) Chandrasekar et al. (2007); (B) To et al. (2007); (C) Alsop and Vijayan (2008).

Adenohypophysis

The adenohypophysis, otherwise known as the anterior pituitary, is an endocrine gland that sits just below the hypothalamus and is integrally associated with the neurohypophysis (posterior pituitary). The adenohypophysis synthesizes and secretes a suite of peptide tropic hormones into the circulation, including ACTH, that together exert endocrine control over nearly every physiological process. ACTH is cleaved from the prohormone proopiomelanocortin (pomc) in specialized cells called corticotropes. In zebrafish, corticotropes are first evident in the developing pituitary as early as 18 hpf. By 48 hpf, a cluster of cells strongly expressing *pomc* are easily distinguished in the adenohypophysis (To et al., 2007) (**Fig. 1B**).

Interrenal cells

In adult fishes, interrenal cells are clustered around the posterior cardinal vein in the anterior (head) kidney. Circulating ACTH binds to melanocortin 2 receptors (mc2r) on the interrenal cell membranes, which initiates the synthesis and secretion of cortisol. A comprehensive review on interrenal cell development was recently published (Bacila et al., 2021), and key points are summarized here. Interrenal cells are derived from mesoderm and are first distinguished by localized expression of the steroidogenic factor, *ff1b*, in a single cell cluster at 22 hpf (To et al., 2007). The interrenal cells continue to proliferate and migrate to form distinct bilateral clusters of cells in the anterior kidney from 48 hpf and beyond (**Fig. 1**B). Transcription of genes encoding several proteins essential for the initial steps of cortisol synthesis occurs early in interrenal cell development. Specifically, *steroidogenic acute regulatory protein* (*star*; transports cholesterol across the mitochondrial membranes and is the rate-limiting step in steroid hormone synthesis), *cytochrome P450 side-chain cleavage* (*cyp11a*; converts cholesterol to pregnenolone), and *3β-hydroxysteroid dehydrogenase* (*hsd3b*; converts pregnenolone to progesterone) are all expressed by 24 hpf. Expression of *11b-hydroxylase* (*cyp11c*; the final enzyme involved in cortisol synthesis), however, does not peak until around hatching, when *mc2r* and *gr* expression also peak, and this coincides with a rise in basal whole-body cortisol levels (Alsop and Vijayan, 2008) (**Fig. 1**C). Indeed, hatching serves as a benchmark for endogenous cortisol production in a variety of fish species (Hwang et al., 1992; Sampath-Kumar et al., 1995; Stouthart et al., 1998) and rapidly increases as the fish approaches the onset of endogenous feeding (Alderman and Bernier, 2009; Alsop and Vijayan, 2008; Fuzzen et al., 2011; Whitehouse et al., 2020).

Integration of the HPI axis

The capacity for young fish to launch an endocrine stress response marks an important transition toward active and integrative homeostatic regulation. Before this can occur, individual components of the HPI axis must communicate, and negative feedback mechanisms must be in place. Here, the genetic and molecular tools available for zebrafish studies, including targeted gene knockdown and knockout experiments (via morpholinos and CRISPR-Cas9, respectively), have helped shed some light on the timing of HPI axis integration during ontogeny.

HPI axis maturation requires that the interrenal cells can respond to trophic signals from the adenohypophysis and that this stimulatory signaling can be regulated through negative feedback by cortisol to the corticotropes. A key step in this communication is the expression of the ACTH receptor, *mc2r*, by interrenal cells, which occurs around 36 hpf in zebrafish, sometime after expression of key steroidogenic enzymes (*cyp11a*, *star*, *hsd3b*) is initiated in these cells (To et al., 2007). Zebrafish mutants that lack anterior pituitary cells, including corticotropes, fail to synthesize *pomc* and release ACTH. During the first 2 days post fertilization (dpf), expression of steroidogenic enzymes and *mc2r* in the interrenal cells is similar in these mutants to wildtype zebrafish; however, by 5 dpf, the absence of ACTH signaling from the pituitary greatly reduces interrenal cell expression of steroidogenic enzymes and *mc2r*. This phenotype was replicated using antisense morpholinos to knockdown the expression of *mc2r*, demonstrating that trophic signaling of pituitary-derived ACTH is needed to maintain the functional integrity of the interrenal cells past 2 dpf (To et al., 2007). In this same study, zebrafish embryos reared in the presence of the synthetic GR agonist dexamethasone showed reduced *pomc* expression in the adenohypophysis at 2 dpf and a clear decline in pituitary *pomc* and interrenal cell *cyp11a* expression between 3 and 5 dpf (To et al., 2007). This highlights that cortisol can exert negative feedback on the corticotropes prior to hatching. Combined, this study demonstrates that reciprocal communication between the pituitary and interrenal cells plays an essential role in the final stages of HPI axis maturation and that this does not occur prior to 2 dpf (**Fig. 2**).

Functional maturation of the HPI axis also requires that hypothalamic CRF neurons are integrated into the sensory circuits that convey stress signals to the brain, that corticotropes express CRF receptors, and that negative feedback by cortisol can act on the hypothalamic CRF neurons. While mutants lacking CRF or the type 1 CRF receptor have been generated (Faught and Vijayan, 2022; Wagle et al., 2011), the timing of functional hypothalamic integration into the HPI axis has yet to be explicitly investigated. Thus, the complete integration of all HPI axis components must be inferred from studies exploring the onset of stressor responsiveness.

In general, fish are not able to increase cortisol in response to a stressor until after hatching is complete. In zebrafish, for example, the anatomy of the HPI axis is formed in the first 24 hpf, key genes are localized in its structures well before 48 hpf, and *de novo* cortisol synthesis is apparent by hatching (**Fig. 2**); yet, even with all these parts in place, 48 hpf zebrafish larvae are unable to respond to a stressor by increasing cortisol levels. The earliest evidence of a stressor-induced increase in cortisol was demonstrated in 72 hpf larvae exposed to an acute osmotic stressor (Alderman and Bernier, 2009). However, increased cortisol production

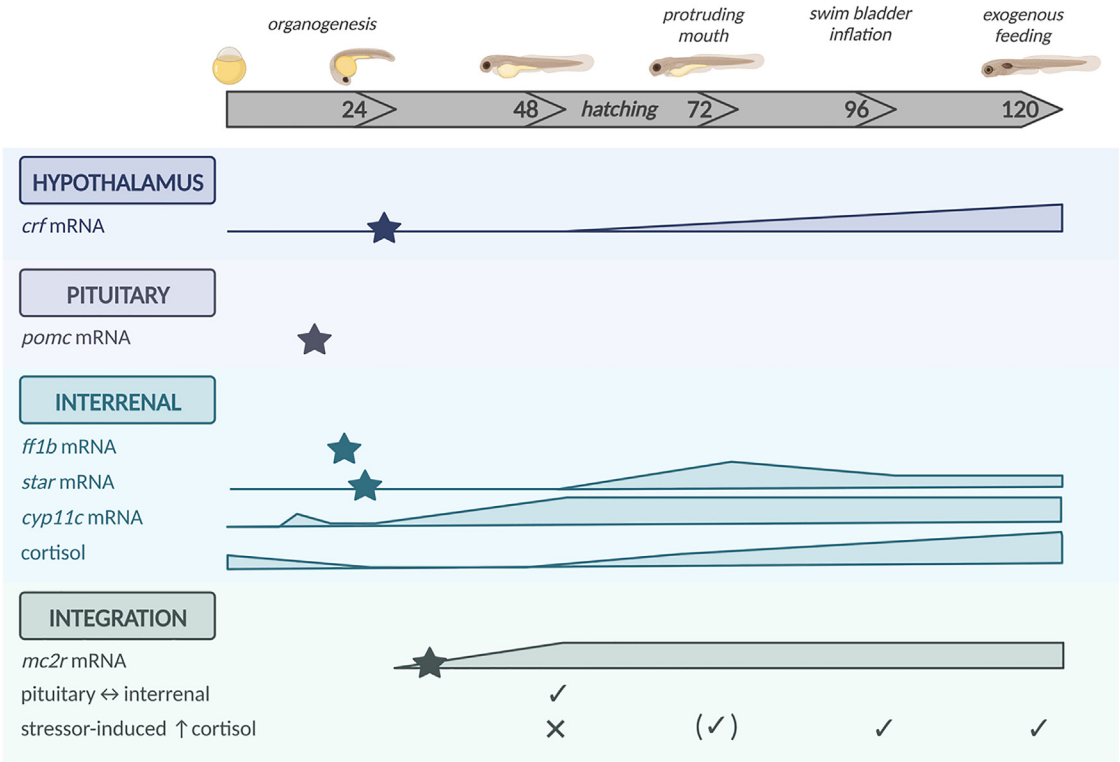


Fig. 2 Summary of HPI axis ontogeny in zebrafish. Select developmental milestones are indicated along a time axis from fertilization to exogenous feeding, encompassing the first 120 h post-fertilization (hpf). The expression of key genes relevant to HPI axis function is indicated either as bars of varying thickness to represent relative abundance changes through time or as stars where mRNA expression was localized within the relevant structure. Evidence of integration within the HPI axis includes trophic signaling and negative feedback between the pituitary and interrenal cells, respectively (checkmark), as well as whether or not a stressor can induce an increase in cortisol (checkmark or ex). In parentheses, the post-stress increase in cortisol at 72 hpf may be stressor-specific, as this was shown to occur with an osmotic stressor but not with mechanical agitation. See text for references. *crf*, corticotropin-releasing factor (stimulates ACTH secretion from the pituitary); *cyp11c*, 11b-hydroxylase (final enzyme in cortisol synthesis); *ff1b*, steroidogenic factor (transcription factor essential for interrenal cell development); *mc2r*, melanocortin receptor (ACTH receptor); *pomc*, proopiomelanocortin (precursor of ACTH); *star*, steroidogenic acute regulatory protein (rate-limiting enzyme in cortisol synthesis). Created with BioRender.com.

following a mechanical stressor was not evident at 72 hpf but could be induced at 96 hpf (Alsop and Vijayan, 2008). This suggests that the maturation of sensory-specific neural circuits may be an additional factor determining when a larval zebrafish can activate the HPI axis in response to specific stressors. A similar developmental pattern holds for other fish species, such as rainbow trout (*Oncorhynchus mykiss*) and yellow perch (*Perca flavescen*), with stressor-induced increases in cortisol occurring after hatch and not before (Barry et al., 1995; Fuzzen et al., 2011; Jentoft et al., 2002). This delay between the apparent maturation of the HPI axis and its activation in response to a stressor suggests that the early life stages of fish have a stress hyporesponsive period, like what is known to exist in mammals. Cortisol is a genomically active pleiotropic hormone, meaning it works by modifying gene expression in target cells that are present in many different tissues. In this way, cortisol can exert a considerable influence on early ontogenic events that follow precisely timed changes in gene transcription. Indeed, studies that have manipulated cortisol signaling during embryogenesis by exogenous treatment with cortisol or synthetic GR agonists report profound effects that include impaired morphogenesis of skeletal muscles, cardiac defects, and heart dysfunction (Nesan et al., 2012; Nesan and Vijayan, 2012; Wilson et al., 2015), as well as changes to larval behaviors, and HPI axis function (Best and Vijayan, 2017; D'Agostino et al., 2019). Thus, the long-held rationale of a stress hyporesponsive period is that it protects the organism from the potentially deleterious effects of elevated cortisol during critical developmental windows. The mechanisms that orchestrate this stress hyporesponsive period are not known.

The zebrafish model has yielded comprehensive insight into the development of the endocrine stress response; however species-specific differences in HPI axis ontogeny cannot be ignored. For example, there are a few examples of a cortisol response elicited prior to hatch. Common carp (*Cyprinus carpio*) embryos increase cortisol in response to a handling stressor just before hatching (Stouthart et al., 1998). A recent study in lake whitefish (*Coregonus clupeaformis*) provides evidence of a narrow developmental window of HPI axis responsiveness early in embryogenesis—at the eyed stage when the heart begins to beat—followed by a characteristic hyporesponsive period lasting until after hatch (Whitehouse et al., 2020).

The maternal effect

Cortisol has been detected in spawned eggs of numerous fish species. As a lipophilic hormone, cortisol can readily diffuse between maternal circulation and follicles. Using a variety of approaches to experimentally manipulate egg cortisol content or cortisol signaling in early development, studies have shown that maternally-deposited cortisol regulates gene expression patterns in early embryogenesis. Examples include genes that support the morphogenesis of major organ systems, including the nervous and musculoskeletal systems, as well as multiple genes associated with the HPI axis (i.e., *crf*, *pomc*, *mc2r*, *star*, *cyp11c*) (Nesan and Vijayan, 2013, 2016). Thus, it is perhaps not surprising to learn that maternal stress, and the consequential increase in circulating cortisol, can lead to increased egg cortisol levels that drive phenotypic changes in offspring. For example, in zebrafish (Jeffrey and Gilmour, 2016), rainbow trout (Auperin and Geslin, 2008), and sockeye salmon (*O. nerka*; Sopinka et al., 2015) offspring born from stressed mothers show an attenuated responsiveness to stress at later life stages. Other studies in zebrafish have shown that increasing egg cortisol content via maternal stress (Higuchi, 2020), cortisol microinjection (Best and Vijayan, 2017), or exogenous cortisol application (D'Agostino et al., 2019) alter neurogenesis and affect larval behavioral phenotypes. Given the propensity for maternally-derived cortisol to influence offspring phenotype, the hypothesis is that variation in egg cortisol content provides a mechanism by which maternal experience can promote environment-phenotype matching in offspring. In a highly stressful environment, for example, it may be metabolically advantageous in the long run for offspring to have a higher stress tolerance threshold.

Zebrafish are continuous spawners, and ovaries contain follicles at various stages of maturation at any given time. Therefore, the timing of maternal stress relative to ovulation can influence the resulting offspring phenotype. In one study, female zebrafish were fed a low dose of cortisol for 5 consecutive days, and then egg cortisol content was compared across daily spawning events for the next 10 days. Increased egg cortisol levels were not observed until the third spawning day and dropped substantially thereafter, implicating maximal cortisol transfer during vitellogenesis (Faught et al., 2016). In another study, two weeks of diel cycles of hypoxia and thermal stress increased ovarian cortisol levels, yet 1 hpf embryos collected from these mothers had less cortisol than those from unstressed mothers (Lim and Bernier, 2022). This suggests that cortisol transfer from the mother to the eggs is regulated within the ovarian tissues of the mother, by the oocytes themselves, or some combination of the two. For example, the degradation of cortisol by catabolic enzymes, including 11β-hydroxysteroid dehydrogenase 2 (hsd11b2; inactivates cortisol to cortisone), may regulate maternal cortisol transfer in several ways. In zebrafish, hsd11b2 enzymatic activity can be measured in zebrafish ovary homogenates (Alderman and Vijayan, 2012), and its mRNA abundance increased in the follicles of females fed a cortisol-supplemented diet (Faught et al., 2016). Similarly, in oocytes harvested from tilapia (*Oreochromis mossambicus*), hsd11b2 activity was demonstrated in the thecal and granulosa cells of the follicle and acted to buffer cortisol entry into the oocyte (Tagawa et al., 2000). In addition to cortisol catabolism, cortisol can be actively extruded from the intracellular compartment via non-specific ATP-binding cassette (ABC) transporters in the cell membrane. Indeed, transcript abundance of an ABC transporter, as well as *hsd11b2*, were elevated in 1 hpf zebrafish embryos from stressed zebrafish mothers (Lim and Bernier, 2022). Combined, these studies suggest that a complex regulatory system determines when and how the context of maternal stress, in the form of cortisol, is transferred to offspring.

Maternal stress can also affect offspring phenotype independently of cortisol transfer. For example, despite the chronic stress associated with social subordination in zebrafish, egg cortisol content was similar in clutches spawned from socially subordinate, socially dominant, and group-housed (neutral social rank) females, nor did clutch size or viability differ in these groups. Nevertheless, the mother's social status accounted for variation in the expression of several HPI axis transcripts measured in larvae aged 48−144 hpf. Differences in transcript abundance were most frequently observed in offspring from dominant mothers and included a decrease in *crf* at 48 hpf and an increase in *star* at 96 hpf. When these offspring were exposed to a handling stressor at 96 hpf, only offspring from subordinate mothers increased cortisol levels. In contrast, the same stressor at 144 hpf activated the HPI axis in all treatment groups but was attenuated in offspring from subordinate mothers (Jeffrey and Gilmour, 2016). These results highlight that maternal experience can influence HPI axis ontogeny and responsivity, although the mechanisms and long-term consequences of these changes await investigation.

Maternal transfer of HPI axis-related gene transcripts to the oocyte during oogenesis may be one mechanism for non-cortisol mediated maternal effects on offspring phenotype. For example, *crf* transcripts are present in freshly spawned eggs, indicating maternal transfer (Alderman and Bernier, 2009; Fuzzen et al., 2011). Whether maternal stress influences the rate of gene transfer into egg follicles has not been shown. Still, variation in the abundance of these genes could be important in early development given recent findings describing a novel function for CRF in mitigating stress-induced apoptosis (Alderman et al., 2018). In zebrafish embryos exposed to a heat shock stressor, the induction of caspase-3 (a marker of apoptosis) coincides with changes in whole embryo *crf* transcript abundance. When additional *crf* is injected into fertilized oocytes, the induction of caspase-3 activity following heat shock is significantly reduced (**Fig. 3**A). Conversely, caspase-3 induction is exacerbated when embryos are recovered from heat shock in the presence of a CRF receptor antagonist, antalarmin (**Fig. 3**B). Combined, these results implicate CRF in minimizing stress-induced apoptosis during early development (Alderman et al., 2018); therefore, variation in the maternal transfer of *crf* transcripts could bestow additional stress tolerance to offspring prior to maturation of the HPI axis.

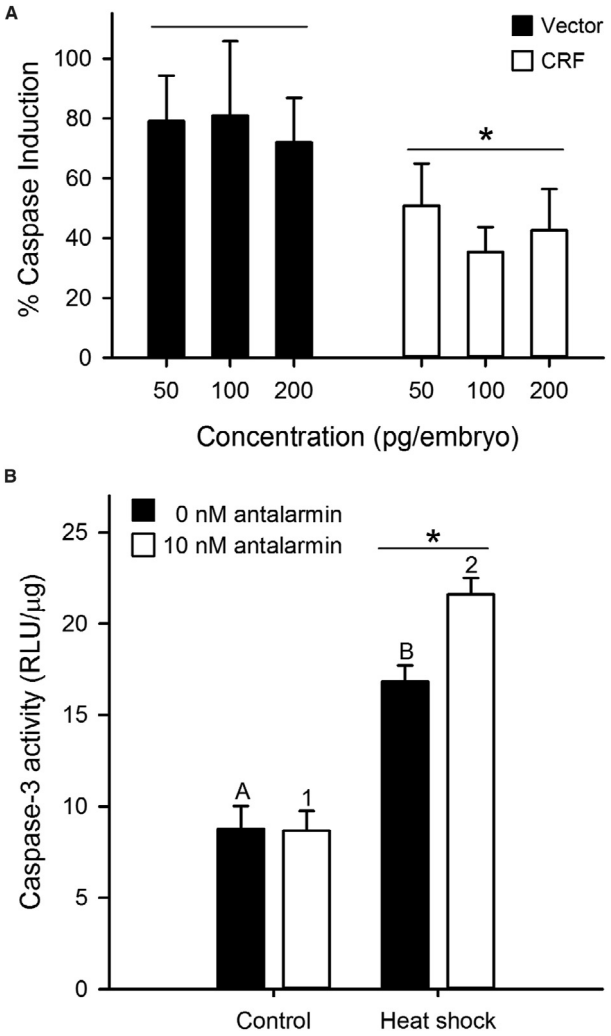


Fig. 3 Corticotropin-releasing factor (CRF) attenuates heat shock-induced apoptosis during early zebrafish development. The stressor was a 1 h heat shock at 40 °C followed by a 10 h recovery at 28.5 °C. (A) Caspase-3 induction, shown as percent change over non-heat shocked controls, in embryos microinjected with varying concentrations of control mRNA or *crf* mRNA. (B) Caspase-3 induction (in relative light units, RLU/μg protein) following heat shock was significantly higher when embryos were recovered in the presence of the CRF-R1 antagonist, antalarmin. Source: All data were analyzed using a two-way ANOVA and Holm-Sidak multiple comparisons test ($p < 0.05$). Images are from Alderman et al. (2018).

Conclusion

Growing up has always been challenging, but this may be more relevant now than ever before. Animals in the natural world are experiencing stressors of increasing magnitude, frequency, and novelty as human activities facilitate a rapid shift in the Earth's climate and land use. For fish, these stressors include rising temperature, falling pH, expanding hypoxic zones, and pollution, among others. This article summarized the developmental time course through which the endocrine system matures and can be recruited to effect homeostatic regulation in response to these stressors. With this information, scientists and conservation biologists can begin to recognize when species are most sensitive to environmental influences in ways that may impact their overall fitness. What is clear from zebrafish studies is that morphological development of the HPI axis happens early in organogenesis, and many molecular components of the HPI axis, such as CRF and cortisol, influence embryo phenotype. In fact, female zebrafish are known to transfer CRF and cortisol into oocytes prior to ovulation, which may provide an important mechanism for matching offspring phenotype to the environment it is born into. From a conservation perspective, the stress hyporesponsive period after hatching is perhaps most relevant in terms of HPI axis ontogeny. In most fishes studied to date, endogenous synthesis of cortisol is evident by the time a fish hatches, yet there is a time delay before a stressor can activate the HPI axis. This stress hyporesponsivity is thought to protect young larvae from excess cortisol signaling during sensitive periods of development.

See Also: Endocrine stress axis and regulation of energy metabolism in chondrichthyes; Endocrine structures and organs; Multiple stressors-physiological responses to multivariate environments; The diversity of reproductive styles exhibited by fish; The hypothalamic-pituitary-interrenal axis and corticosteroids; The pituitary gland of fishes.

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