Stress Hormones and Human Developmental Plasticity:

Lessons From Tadpoles

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Author Disclosure
Drs Denver and Crespi did not disclose any financial relationships relevant to this article.

Objectives

After completing this article, readers should be able to:

1. Define phenotypic plasticity.
2. Delineate the roles of stress hormones in controlling the timing of life history transitions and phenotypic outcomes.
3. List the long-term phenotypic consequences of exposure to stress early in life.

Introduction

Phenotypic expression depends on the interaction between the genotype (nature) and the environment (nurture). This is true for all living organisms, but the physiologic mechanisms that mediate this interaction remain poorly understood. Very early developmental events generally are regarded as being buffered from environmental effects (ie, they are canalized), but it is now clear that the earliest environment experienced by the embryo can shape developmental outcomes, that is, result in developmental plasticity or prenatal programming. For example, the probability of preterm birth is highly correlated with the experience of stress during the periconceptional period. Thus, fetal development tends to be more variable in timing and possibly more susceptible to environmental influences.

Phenotypic Plasticity

The environment influences development by modifying morphology and physiology, thus resulting in specific phenotypic outcomes, and modifying the timing of developmental events. The term "phenotypic plasticity" is used to describe the process by which organisms modify their development, behavior, or physiology in response to changing environments. Phenotypic plasticity has been described in almost every group of plants and animals, and it can have important fitness consequences. For example, it may be adaptive if it leads to increased survival during the embryonic or larval life stage. Yet, there are important tradeoffs associated with phenotypic plasticity. For example, amphibian tadpoles may accelerate metamorphosis in response to a deteriorating larval habitat (eg, a drying pond, high density of predators, low food) and, thus, increase the probability of immediate survival through metamorphosis. However, this accelerated development comes at a cost: decreased growth and smaller body size at transformation that may lead to reduced survival and reproductive capacity later in life.

In humans, the intrauterine environment has profound effects on fetal growth, development, and the timing of birth. Amphibians and humans (ie, mammals) differ in how these early environmental effects are experienced, especially because amphibian tadpoles are free-living compared with mammals that develop within a womb. Nevertheless, the basic developmental and physiologic mechanisms that underlie developmental plasticity arose early in vertebrate evolution and are largely conserved today in extant amphibians and mammals.

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Amphibians

Amphibians exhibit extreme plasticity in the timing of metamorphosis that is related directly to conditions in the larval habitat and, thus, growth opportunities. Amphibian ecologists have shown that biotic factors such as population density, food availability, predator presence, and water level, singly or in combination, can influence the timing of and size at metamorphosis. Furthermore, abiotic factors such as temperature, dissolved gases, pH, and photoperiod interact in complex ways with biotic factors to affect development. The availability of water is arguably the single most important environmental variable for an aquatic organism such as a tadpole (and consider the aquatic environment of the human fetus). Amphibian species that breed in unpredictable habitats (eg, arid habitats) show phenotypic plasticity in response to pond drying (Fig. 1). A decrease in the water volume of aquaria in which tadpoles are reared can accelerate metamorphosis, which is a reflection of the tadpole's response to a drying pond in nature. Tadpoles can vary the rate of the response with respect to the rate of water volume reduction.

For a tadpole, the rates of development and growth tend to be inversely related. Thus, a faster development rate generally is correlated with a smaller body size at metamorphosis (Fig. 1). If conditions in the larval habitat are favorable for growth, tadpoles continue to capitalize on such opportunities, thus delaying metamorphosis. However, if growth conditions deteriorate, tadpoles accelerate metamorphosis on reaching a threshold body size/stage of development. In a deteriorating larval habitat, early metamorphosis can increase chances for immediate survival and allow individuals to access an alternate ecologic niche in which growth opportunities might be more favorable. However, with accelerated metamorphosis, the maximization of growth is traded off for faster development, which can have important fitness consequences, such as lower postmetamorphic survival, reduced body size at first reproduction, and delayed reproductive maturity.

A similar tradeoff between growth and development is observed in mammals. For example, intrauterine stress resulting from maternal malnutrition or hypoxia often leads to fetal growth restriction and preterm birth. Such accelerated development may be adaptive in that it can increase chances for immediate survival by escaping a deteriorating intrauterine environment. However, this is traded off with low birthweight, increased morbidity, greater demands for maternal care, and negative health consequences expressed later in life, such as increased risk for hypertension, type 2 diabetes, and obesity.

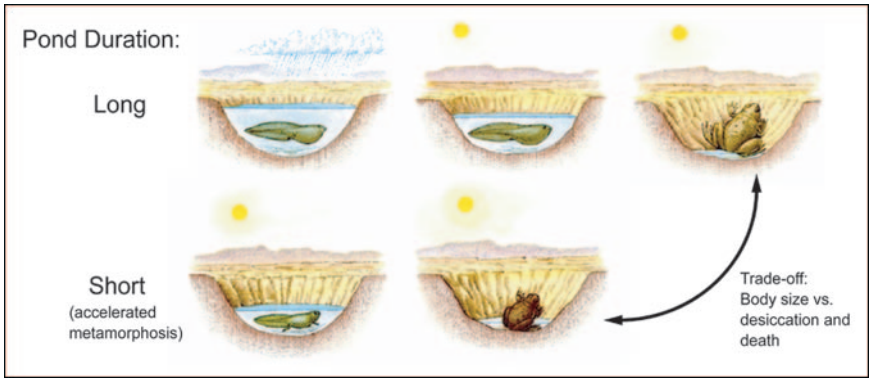

Figure 1. Accelerated metamorphosis induced by pond drying results in tradeoffs between maximization of body size at metamorphosis and immediate survival in the larval habitat. Body size is correlated positively with measures of Darwinian fitness in the adult. Figure modified with permission from Smith R. Timing of birth. *Sci Amer.* 1999;280:68–75.

Stress Hormones and Development

The neuroendocrine system transduces environmental information into developmental and physiologic responses. Recent findings show that stress hormones of the hypothalamic-pituitary-adrenal (HPA) axis play a central role in the timing of life history transitions and can have profound organizational effects on the developing fetus, often referred to as "fetal programming." The HPA axis is activated in response to physical or emotional stress, leading to a rapid increase in plasma glucocorticoid concentration. The production of glucocorticoids by the adrenal cortex is controlled by pituitary adrenocorticotropic hormone (ACTH), which is controlled by hypothalamic corticotropin-releasing factor (CRF). The expression of CRF in the hypothalamus and its stimulatory action on ACTH secretion is common to all vertebrates. Besides their central role in the endocrine stress response, CRF-like peptides also serve to integrate the autonomic and behavioral responses to stress via actions within the central nervous system. Although chronic or excessive activation of the HPA axis during juvenile or adult life can lead to serious health problems, this response evolved as an essential adaptive system to allow for the maintenance of homeostasis. Recent work has shown that elevations in corticosteroids during early development can

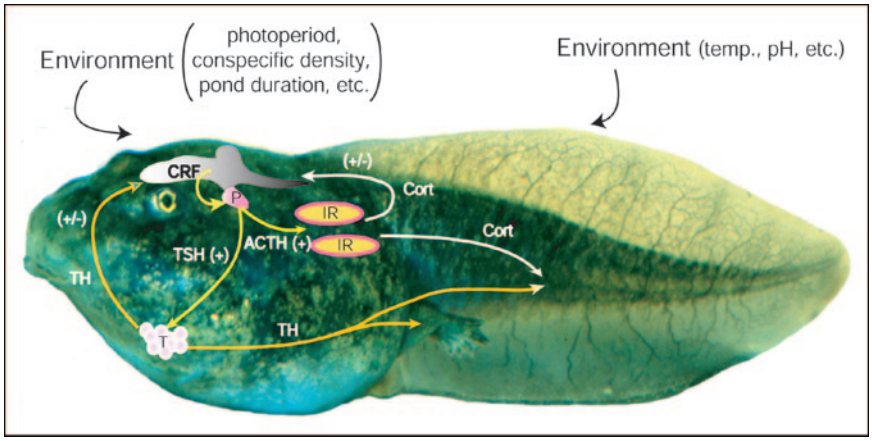

Figure 2. Endocrine systems that control tadpole metamorphosis. P=pituitary gland, CRF=corticotropin-releasing factor (CRF regulates both TSH and ACTH secretion in tadpoles), IR=interrenal gland (homologous to mammalian adrenal cortex), ACTH=adrenocorticotropic hormone, TSH=thyroid-stimulating hormone, T=thyroid gland, TH =thyroid hormone, Cort=corticosteroids, +=a stimulatory effect, -=a negative feedback. In the case of TH and Cort effects on the brain, (+/-) indicates that these hormones promote differentiation of neurosecretory centers (and other brain regions) in addition to their negative feedback effects on neurohormone and pituitary hormone secretion. Reprinted with permission from Denver RJ, Boorse GC, Glennemeier KA. Endocrinology of complex life cycles: amphibians. In: Pfaff D, Arnold A, Etgen A, Fahrbach S, Rubin R, eds. *Hormones, Brain and Behavior.* San Diego, Calif: Academic Press; 2002:469 with permission from Elsevier.

result in widespread effects on growth and development that can permanently alter physiology and morphology.

Tadpole Metamorphosis

Tadpole metamorphosis depends on thyroid hormone (T_3) (Fig. 2). As is true for all gnathastome (jawed) vertebrates, the tadpole's hypothalamus regulates pituitary thyroid-stimulating hormone (TSH) secretion that, in turn, controls the thyroid gland. Thyrotropin-releasing hormone (TRH), the first hypophysiotropic peptide isolated, is the principal TSH-releasing factor in mammals. However, despite its presence in the brains of larval and adult amphibians, TRH does not influence TSH secretion by the tadpole pituitary or affect metamorphosis. In addition to their actions on ACTH release, CRF peptides are potent stimulators of the thyroid axis through direct actions on pituitary TSH secretion in amphibians and other nonmammalian species. It is also important to note that glucocorticoids can synergize with T_3 to accelerate tissue transformation by upregulating T_3 receptors in target tissues, and T_3 can regulate glucocorticoid receptor expression. Thus, there are important interactions between the thyroid and adrenal axes in animal development, involving a common central neuroregulator of the two endocrine axes (CRF peptides) and cross-regulation of nuclear receptors by T_3 and glucocorticoids in target tissues.

The environment can influence the activity of the tadpole's neuroendocrine stress axis soon after hatching. The production of T_3 and glucocorticoids increases during spontaneous metamorphosis or can be elevated by exposure to certain environmental factors that may be considered stressors (eg, habitat desiccation, crowding and resource restriction). These observations led us to hypothesize that environmental stress, acting via the neuroendocrine system, can accelerate metamorphosis and, thus, minimize the risk of mortality in a rapidly deteriorating environment.

The consequences of stress system activation for growth and development of tadpoles vary, depending on the duration and developmental stage during which the stressor is experienced. Tadpoles at early developmental stages slow growth and development in response to adverse environmental conditions, a response that is at least partially mediated by adrenal steroids. When conditions improve, tadpoles can resume growth but ultimately metamorphose at a later date. By contrast, for tadpoles in late stages of larval development, adverse environmental conditions (eg, pond drying, interspecific competition for resources, predator presence) lead to accelerated metamorphosis. This competency to respond to the environmental cue by accelerating development is correlated with the development of neurosecretory cells in the hypothalamus, maturation of the median eminence (the structure that delivers neurohormones to the pituitary gland), and expression of neuropeptide receptors in pituitary cells. This response is adaptive, especially for those amphibian species that live in arid climates where the capacity to track the environment and respond accordingly is critical to avoid desiccation and death in a drying pond.

Tadpoles of the Western spadefoot toad (*Spea hammondii*) accelerate metamorphosis in response to pond drying or food restriction. Such acceleration is associated with precocious activation of the neuroendocrine system, as evidenced by elevated production of hypothalamic CRF, T_3, and glucocorticoids. The developmental re-

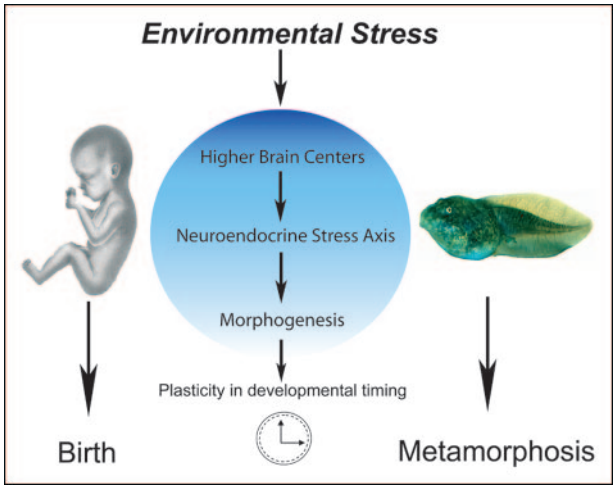

Figure 3. The environment (intrauterine or pond) influences the timing of life history transitions through the evolutionarily conserved actions of stress hormones. Unlike the tadpole, which is a free-swimming animal, the human fetus is influenced by hormones of maternal and placental origin. Reprinted with permission from Crespi EJ, Denver RJ. Ancient origins of human developmental plasticity. *Am J Human Biol.* 2005;17:44–54.

sponse depends on endogenous CRF because it can be blocked by CRF antagonists or passive immunization with CRF antiserum. Because T_3 and glucocorticoids synergize to control metamorphosis, the common central regulation of these two endocrine systems by CRF allows tadpoles to modulate their rate of development in response to a changing environment.

Human Development and the Timing of Parturition

CRF and glucocorticoids now are known to play critical roles in the timing of birth in mammals (Fig. 3). A considerable body of literature now supports the hypothesis that the timing of human parturition is driven by the upregulation of CRF and glucocorticoids, a signal originating in the fetus that ultimately influences placental hormone production, thus precipitating labor. It is important to note that in addition to timing parturition, such stress hormones also have important developmental actions in the fetus, such as for lung maturation and brain development.

The human fetal HPA axis matures during the third trimester, and maternal circulating concentrations of CRF and glucocorticoids increase, largely due to a positive feedback loop between fetal glucocorticoids and the placenta (glucocorticoids positively regulate placental CRF production). Placental CRF also may stimulate the secretion of fetal adrenal steroids, which further stimulate placental CRF secretion. The outcome of this positive feedback loop is an exponential increase in stress hormones in the mother and the fetus that promote the maturation of fetal organs (eg, brain, lung, gut) and the preparation and stimulation of the myometrium and fetal membranes for parturition.

Exposure to stressors such as maternal malnutrition, hypoxia, or infection can result in precocious maturation of the fetal HPA axis. Owing to the developmental actions of stress hormones, organ maturation may occur earlier at the cost of fetal growth, as observed in larval amphibians. Glucocorticoids are related causally to intrauterine growth restriction in mammals, just as elevated glucocorticoid concentrations reduce tadpole growth. In humans, elevations in maternal plasma CRF concentrations during gestation (driven by placental secretion of CRF) are associated with higher probabilities of preterm birth. However, it is unknown how adverse conditions experienced before conception actually manifest in altered hormone profiles during later gestational stages.

Whether the effects of early elevations of stress hormones (presumably a reflection of a stressful intrauterine environment) on fetal growth and gestational length in humans can be considered adaptive is uncertain. Exposure to glucocorticoids or stress accelerates fetal brain maturation and lung development, which could enhance preterm infant viability. As in the case of tadpoles facing a drying pond, the early escape from a hostile intrauterine environment might accelerate maturation such that the individual can transition to a terrestrial environment where conditions might be more favorable for growth and development. This response depends, of course, on the stage of development, which determines the capacity to mature critical organ systems to survive outside of the womb. The mean gestational length of triplets is shorter than that of twins, which is shorter than singletons, and could be a reflection of competition for resources within the womb. Given the essential neurodevelopmental actions of T_3 and glucocorticoids, it is reasonable to hypothesize that the increase in production of these hormones is the proximate link between stressors that lead to preterm birth and the associated accelerated neurologic development. Although the actions of stress hormones promote preterm birth and may enhance immediate survival, the long-term effects of elevated glucocorticoid concentrations during gestation suggest that the early, immediate survival benefits come at a significant cost.

Long-term Phenotypic Consequences of Early Life Stress

For the tadpole, accelerated metamorphosis can increase the probability of survival in a rapidly deteriorating environment such as a drying desert pool. However, as discussed previously, the resultant smaller body size at metamorphosis is likely associated with future fitness costs. These may include slower growth rates as juveniles, reduced performance (ie, locomotory ability), greater susceptibility to starvation, and higher mortality. In most species, the body size disadvantage at metamorphosis is retained through the age at first reproduction and, thus, can reduce reproductive fitness.

It is interesting to note that the effects of environmental stress on the tadpole are very similar to the effects of intrauterine stress on the mammalian fetus. Maternal malnutrition or exposure to stressors cause intrauterine growth restriction and preterm birth and may lead to reproductive dysfunction and susceptibility to disease later in life. There is now compelling evidence that the later-life effects of stress experienced in utero are caused by exposure of the fetus to elevated glucocorticoid concentrations. These effects include permanent alteration of the functioning of the stress axis and metabolism as well as the expression of abnormal social and food intake behaviors. Maternal nutritional stress in rodents is known to cause increased hypothalamic CRF expression and circulating glucocorticoids and often is associated with hyperphagia and "catch-up growth." Although prenatally stressed humans typically compensate in body size through catch-up growth, they exhibit higher probabilities for hypertension, obesity, and type 2 diabetes. Similarly, reduced food resources for a tadpole results in increased food intake and compensatory growth in the juvenile frog.

Conclusion

We propose that the neuroendocrine stress axis is a phylogenetically ancient signaling system that allows developing animals to track the quality of their habitat and to respond accordingly. This neuroendocrine response results in adaptive physiologic and developmental adjustments that are necessary for immediate survival. However, immediate survival may be traded off with compromised adult measures of fitness, such as abnormal behavior, eating disorders, and susceptibility to disease. Our common evolutionary history and the similar mechanisms that govern development suggest that many of the basic problems of responding to a deteriorating developmental habitat were solved before the evolution of the amniotes. For this reason, comparative studies can help us to understand the origins and adaptive significance of human developmental plasticity.

ACKNOWLEDGMENTS. Basic research from the author's laboratory described in this review was supported by grants from the NSF IBN 9974672 and IBN 0235401 to R.J.D.

Suggested Reading

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NeoReviews Quiz

1. Amphibians exhibit plasticity in the timing of metamorphosis, which is influenced by several biotic and abiotic factors in the larval habitat. Of the following, the *most* important environmental factor to influence metamorphosis in an aquatic organism is:

   A. Dissolved gases.
   B. Environmental temperature.
   C. Population density.
   D. Predator presence.
   E. Water availability.

2. The neuroendocrine system transduces environmental information into developmental and physiological responses. Of the following, the stress-related metamorphosis in amphibians is *most* dependent on:

   A. Growth hormone.
   B. Insulin.
   C. Parathormone.
   D. Thyroid hormone.
   E. Thyrotropin-releasing hormone.

3. The timing of parturition in humans is driven by upregulation of hormones. This signal originates in the fetus and ultimately influences placental hormone production, which precipitates labor. Of the following, human parturition is *most* driven by the upregulation of:

   A. Corticotropin-releasing hormone.
   B. Growth hormone.
   C. Insulin.
   D. Parathormone.
   E. Thyroid hormone.