

*Wiley-Liss Plenary Symposium***Ancient Origins of Human Developmental Plasticity**ERICA J. CRESPI¹ AND ROBERT J. DENVER^{1,2*}¹*Department of Molecular, Cellular and Developmental Biology, The University of Michigan, Ann Arbor, Michigan 48109*²*Department of Ecology and Evolutionary Biology, The University of Michigan, Ann Arbor, Michigan 48109*

ABSTRACT Animals have the ability to alter development, physiology, growth, and behavior in response to different environmental conditions. These responses represent critical assessments of both external and internal factors. For example, the timing of metamorphosis, hatching, or birth depends on the trade-offs between growth opportunity and mortality risk in the developmental habitat. Physiological sensors compute these trade-offs as a function of energy balance and environmental stress, and effectors initiate physiological, developmental, and behavioral responses to these determinations. The neuroendocrine stress axis provides a means for animals to integrate information from multiple sources and to respond accordingly. Considerable evidence now supports the view that the secretion of hormones critical to development (corticosteroid and thyroid hormones) is controlled by a common neuroendocrine stress pathway involving corticotropin-releasing factor (CRF) and related peptides. CRF produced in the hypothalamus stimulates the biosynthesis and secretion of both thyroid and corticosteroid hormones, leading to accelerated tadpole metamorphosis. Similarly, in mammals CRF of fetal and placental origin has been shown to influence the timing of birth. Studies in several experimental animal models and in humans show that early life experience can have long-term phenotypic consequences. Furthermore, there is evidence that phenotypic expression is strongly influenced by the actions of stress hormones produced during development. The integrated neuroendocrine response to stress, and its role in timing critical life history transitions and establishing long-term phenotypic expression, arose early in the evolution of vertebrates. *Am. J. Hum. Biol.* 17:44–54, 2005. © 2004 Wiley-Liss, Inc.

There are numerous examples in animals and plants in which a given genotype can generate multiple phenotypes depending on the environmental conditions experienced by the organism during development (Stearns, 1991). Indeed, recent studies show that the environment experienced by the mother can have profound influence on phenotypic expression in the offspring, and these effects can be transmitted through multiple generations (“maternal environmental effects”) (Champagne et al., 2003; Mousseau and Fox, 1998; Wolf et al., 1998). Similar phenomena have been described in humans (Barker, 1992, 1994; Barker and Clark, 1997; Kaplan, 1954; Lasker, 1969), and the importance of environmental effects during early development for human health has received increasing attention in recent years (Bateson et al., 2004). However, we still understand little about environmental effects on human development, and the underlying developmental and physiological mechanisms.

The morphological, physiological, and behavioral characters of modern humans arose

through hundreds of millions of years of vertebrate evolution. Most of the basic mechanisms that govern human development and physiology are present in primitive extant vertebrates, and even invertebrate species (Denver, 1999; Gilbert and Bolker, 2001; Shubin et al., 1997). Thus, it is not surprising that the adaptive solutions that humans have developed are derived evolutionarily from mechanisms that were in place in the earliest vertebrates. This review will focus on the underlying physiological basis for developmental plasticity as discovered through the study of experimental animals. The vertebrate animals

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that have served as primary models for the study of the roles of hormones in developmental plasticity are rodents, sheep, and amphibians. Two aspects of developmental plasticity will be addressed: 1) the timing of life history transitions (e.g., metamorphosis, birth), and 2) the impact of early life experience on later phenotypic expression. Where possible, parallels will be drawn to mechanisms of human developmental plasticity.

PHENOTYPIC (DEVELOPMENTAL) PLASTICITY: WHAT IS IT?

Phenotypic plasticity is the process by which organisms modify their behavior, morphology, and physiology in response to changing environments, and has been described in almost every group of plant and animal (Via and Lande, 1985). Plastic responses during early development have particularly important fitness consequences since they can lead to permanent and profound modifications of morphology or physiology (Frankino and Raff, 2004; Gilbert, 2001; Nijhout, 2003). Phenotypic plasticity can be adaptive if it increases survival during the embryonic or larval life stage; however, there are trade-offs associated with such plasticity. Alteration in developmental timing can affect traits expressed later in life that result in negative fitness consequences. For example, some amphibian species can accelerate metamorphosis in response to pond drying, thus increasing survival through metamorphosis (Denver et al., 1998; Newman, 1992). Yet, this acceleration in development is associated with a reduction in growth, resulting in smaller body size at transformation that also results in reduced survival and reproductive capacity later in life (Berven, 1983; Semlitsch et al., 1988; Smith, 1987).

Because of their complex life cycles, amphibians are ideal for investigating environmental effects on early development, and their impact on future phenotypic expression and fitness. Although "ecological development" as a biological discipline has been only recently discussed in the literature (Gilbert, 2001; Sultan, 2003), amphibian ecologists have been studying this phenomena for more than 30 years (see Denver et al., 1998; Newman, 1992). These studies have clearly shown that environmental conditions experienced during the larval (i.e., tadpole)

stage, such as conspecific density (i.e., crowding), food availability, habitat desiccation, and exposure to predators have significant effects on body size, morphology, and the timing of metamorphosis (Berven, 1983; Semlitsch et al., 1988; Smith, 1987). Similarly, the intrauterine environment has important effects on fetal growth, development, and the timing of birth in mammals. There are differences in how these early environmental effects are experienced by amphibians and mammals, especially because amphibian tadpoles are free-living compared with mammals that develop within the womb. However, because of a shared evolutionary history, the physiological mechanisms that underlie developmental plasticity in amphibians and mammals, including humans, are likely to be conserved.

Phenotypic plasticity in amphibians

While larval amphibians exhibit plasticity in behaviors and morphological features in different environments (i.e., "polyphenisms"), here we focus on the amazing ability of amphibians to adjust the timing of metamorphosis according to conditions experienced during the larval stage. Within a species, the variance in the timing of transformation can be as high as 90% and is determined by the suite of ecological factors present in the larval habitat (see Denver, 1997b). Field studies have shown that biotic factors such as conspecific density, food availability, predator presence, and water level, singly or in combination, can influence the timing of and size at metamorphosis (reviewed by Boorse and Denver, 2003). Also, several abiotic factors such as temperature, dissolved gases, pH, and photoperiod can interact in complex ways with biotic factors to alter development (Marian and Pandian, 1985; Newman, 1988).

The rate of tadpole development tends to be inversely related to the rate of growth, and thus to size at metamorphosis. That is, if conditions are favorable in the larval habitat tadpoles continue to capitalize on growth opportunities and delay metamorphosis. However, if environmental conditions deteriorate tadpoles have the capacity, after reaching a threshold body size/stage of development, to activate their endocrine systems and accelerate metamorphosis. The earlier transition from the larval to the adult habitat increases chances for immediate survival

(e.g., to escape a drying pond) and allows individuals to access areas where growth opportunities might be more favorable. However, accelerated metamorphosis translates into smaller body size at transformation (i.e., maximization of growth is traded off to faster development). The size at transformation can have important fitness consequences, such that smaller size at metamorphosis results in lower survival (Morey and Reznick, 2001), reduced size at first reproduction, and delayed reproductive maturity (Berven, 1983; Semlitsch et al., 1988; Smith, 1987).

A similar trade-off between growth and development is observed in rodents, sheep, and humans during the fetal stage. Stressful intrauterine conditions, resulting from maternal malnutrition or hypoxia, for example, result in fetal growth retardation and preterm birth. While these growth and developmental responses may be adaptive in terms of increasing survival through birth, intrauterine stress can lead to negative health consequences that are expressed later in life, such as increased risk of hypertension, type II diabetes, and obesity (Barker, 1992; Barker and Clark, 1997; Matthews, 2002).

STRESS HORMONES IN DEVELOPMENT, PHYSIOLOGY, AND BEHAVIOR

The maintenance of homeostasis is a central principle toward which an organism's physiology is directed. Vertebrate animals respond to stress by activating the sympathetic branch of their autonomic nervous system (fight-or-flight response; Selye, 1976) followed by hormone secretion by the hypothalamo-pituitary-adrenal (HPA) axis (Sapolsky et al., 2000; Selye, 1980). Production of corticosteroids by the adrenal cortex (interrenal glands in lower vertebrates) is controlled by pituitary adrenocorticotrophic hormone (ACTH), which is controlled by hypothalamic corticotropin-releasing factor (CRF) (Rivier and Plotsky, 1986; Tonon et al., 1986).

CRF and related peptides (i.e., the urocortins) are expressed in distinct brain regions and peripheral tissues where they control behavioral, morphological, and physiological responses to changing environmental conditions. CRF is synthesized in hypothalamic nuclei and is released in response to stress

at modified nerve terminals in the median eminence, the structure that delivers CRF and other neurohormones to the pituitary gland. The expression of CRF in the hypothalamus and the stimulation of pituitary ACTH secretion by CRF is common to all vertebrates (Denver, 1999). CRF (and urocortins) is also expressed in brain regions outside of the hypothalamus, including the cortex, limbic system and brainstem nuclei, that are associated with autonomic function. In addition to their central role in the endocrine stress response through activation of the HPA axis, CRF-like peptides also serve to integrate the autonomic and behavioral responses to stress via their actions within the CNS (Bernier and Peter, 2001a,b; Lowry et al., 1996; Owens and Nemeroff, 1991; Webster et al., 1998).

Corticosteroids also play integral roles in mediating an animal's response to its environment. Circulating corticosteroid concentrations are elevated in many taxa in response to environmental stress (i.e., food deprivation, extreme weather, exercise, crowding, among others; Licht, 1983; Sapolsky, 2000; Wingfield et al., 1998; Zerani, 1991). Corticosteroids increase metabolic rate and mobilize fuel stores, a response thought to enhance performance during emergency or stressful events (Wingfield et al., 1998). The neuroendocrine system can respond to physical stress by upregulating adrenal corticosteroid secretion even during early stages of development (Glennemeier and Denver, 2002a). Evidence from recent studies of both amphibians and mammals suggest that elevation of corticosteroids during development results in widespread effects on growth and development (Denver et al., 2002; Welberg and Seckl, 2001), and these early effects can permanently alter physiology and morphology (Barker, 1992; Barker and Clark, 1997; Matthews, 2002).

Stress hormones mediate environmental effects on amphibian metamorphosis

Although most studies on the activation of the stress axis and the physiological actions of corticosteroids have focused on the adult stage, stress hormones also play important roles during early development. The stress hormonal axis, acting both centrally and peripherally, can transduce environmental signals into developmental responses. For

example, in amphibian larvae thyroid hormone (T_3) controls metamorphosis and corticosteroids are known to synergize with T_3 to accelerate metamorphosis (Kikuyama et al., 1993). These findings lead to the prediction that stress (during prometamorphosis: characterized externally by hindlimb morphogenesis) will accelerate metamorphosis. This prediction is supported by observations that habitat desiccation, crowding, and resource restriction, all of which elevate corticosteroids, can accelerate metamorphosis (Denver et al., 2002).

Factors that control the production, metabolism, and actions of T_3 determine the timing of metamorphosis. The synthesis and secretion of T_3 is controlled by pituitary thyrotropin (TSH) and TSH is controlled by a hypothalamic thyrotropin-releasing factor (TRF; Denver, 1996). The importance of hypothalamic control of metamorphosis has long been recognized (Denver, 1996; Kikuyama et al., 1993). The tripeptide thyrotropin-releasing hormone (TRH) is the principal TRF in mammals, but despite its presence in the brain of larval and adult amphibians, TRH does not influence tadpole metamorphosis (Denver, 1996; Kikuyama et al., 1993).

Considerable evidence now supports a role for CRF as a larval amphibian TRF and controller of metamorphosis (Denver, 1999). CRF is a 41-amino acid polypeptide first isolated for its ability to stimulate ACTH secretion in mammals (Turnbull and Rivier, 1997; Vale et al., 1981). Studies of ours and others showed that CRF is a potent TRF in non-mammalian species including tadpoles (Denver and Licht, 1989a,b, 1991; Denver, 1988, 1999; Kuhn et al., 1998; Larsen et al., 1998). CRF accelerates metamorphosis through its combined actions on T_3 and corticosteroid production (reviewed by Boorse and Denver, 2003). Thus, the thyroid and the HPA axes can interact at both central and peripheral levels to influence the timing of metamorphosis (Denver, 2002).

In mammals, thyroid hormone is known to play a critical role in development, particularly that of the brain (i.e., thyroid deficiency during development results in cretinism; Porterfield and Hendrich, 1993). It is noteworthy that daily handling of neonatal rats for brief periods (i.e., handling stress) increases plasma T_3 concentration in rats, and Meaney et al. (2000) showed that T_3 is required for the increase in hippocampal

glucocorticoid receptor (GR) expression observed following exposure to handling stress. The hippocampus is an important site for the mediation of negative feedback by glucocorticoids on CRF expression, and increased hippocampal GR is associated with diminished stress axis reactivity (Meaney, 2001). These findings provide evidence for a linkage between the thyroid and HPA axes in developing animals, but much remains to be learned about this relationship.

Tadpoles can activate the neuroendocrine stress axis in response to environmental factors soon after hatching. The growth and developmental consequences of stress system activation vary depending on the duration and developmental stage during which the stressor is experienced. In premetamorphosis (i.e., before hindlimb and thyroid gland development; Denver et al., 2002), tadpoles slow development in response to adverse environmental conditions (Glennemeier and Denver, 2002b, c; Hayes, 1997). We have found a role for corticosteroids in the negative growth response of tadpoles to intraspecific competition (Glennemeier and Denver, 2002c). If the stressor is removed, tadpoles can resume growth but will ultimately metamorphose at a later date.

By contrast, during later tadpole stages as metamorphic climax approaches and when the neurosecretory cells in the hypothalamus and the median eminence have matured, environmental stress can accelerate metamorphosis. This response is adaptive, especially in amphibian species that live in arid climates where pond drying will inevitably result in mortality if the tadpoles do not alter their rate of development. We found that prometamorphic tadpoles of the Western spadefoot toad accelerate metamorphosis in response to water volume reduction or food restriction, and that this acceleration was associated with precocious elevations in hypothalamic CRF and whole-body thyroid hormone and corticosterone content (Boorse and Denver, 2003; Crespi and Denver, 2004b; Denver, 1997a, 1998). Furthermore, we provided direct evidence that CRF plays a central role in the metamorphic response to pond drying (Denver, 1997a). Because thyroid hormone and corticosterone work synergistically to remodel tissues and mature organs needed for the transition to terrestrial life (Hayes, 1997; Kikuyama et al., 1993; Krain and Denver,

2004), the common regulation of these two peripheral endocrine systems by CRF allows tadpoles to modulate their rate of development in response to a changing environment.

Stress hormones and the timing of human birth

In mammals recent evidence points to a critical role for CRF and corticosteroids in the timing of birth. In humans, the timing of parturition appears to be driven by the upregulation of CRF and adrenal steroids in the fetus. A role for corticosteroids of maternal origin and CRF of placental origin in the timing of birth has also been postulated (Hillhouse and Grammatopoulos, 2002; McLean and Smith, 2001). The mammalian HPA axis normally matures during mid- to late gestation, depending on the species (third trimester in humans). As birth approaches, maternal circulating concentrations of both CRF and corticosteroid increase largely due to a positive feedback loop between the placenta and fetus (Hillhouse and Grammatopoulos, 2002; McLean and Smith, 2001). Placental CRF stimulates the secretion of fetal adrenal steroids, which travel via umbilical cord circulation to the placenta, where they further stimulate CRF secretion. The ultimate outcome is an exponential increase in stress hormones in the mother and fetus that promote 1) maturation of fetal organs required for the transition from an aquatic to a terrestrial existence (e.g., brain, lung, gut), and 2) preparation and stimulation of the myometrium and fetal membranes for parturition (although the specific mechanisms linking CRF with the onset of uterine contraction are still unclear; Challis et al., 2001).

Stressors such as maternal malnutrition, hypoxia, or infection cause precocious maturation of the fetal HPA axis, partially as a result of exposure to CRF and corticosteroids from maternal or placental sources, and can affect fetal development throughout gestation. Because of the developmental effects of these hormones, organ maturation occurs more rapidly at the cost of fetal growth as observed in larval amphibians. Indeed, experimental manipulations have shown that corticosteroids are causally related to intrauterine growth retardation in mammals (Jensen et al., 2002), just as elevated corticosteroids reduce tadpole

growth (Glennemeier and Denver, 2002b, c). Stress experienced early in fetal development is associated with a reduced length of gestation (i.e., preterm birth). The probability of preterm birth increases even when stressors are experienced during the periconceptional period (Bloomfield et al., 2003; Edwards and McMillen, 2002). Similarly, early elevation in maternal circulating CRF during gestation (driven by placental secretion of CRF) has been associated with higher probabilities of preterm birth in humans (i.e., the "CRF placental clock"), and assays of maternal blood CRF concentration have been proposed as a diagnostic test to identify women at risk for preterm labor (McLean et al., 1995).

By contrast, stressors that elevate fetal exposure to corticosteroids during late gestation are more likely to result in intrauterine growth retardation (Hobel and Culhane, 2003; Lesage et al., 2004). For example, pregnant females that experienced the Dutch famine of 1944–45 during early gestation had a higher frequency of preterm births relative to control cohorts, while those that experienced the famine during late gestation had lower fetal birthweights but normal timing of birth (Hobel and Culhane, 2003; Stein and Susser, 1975; Susser and Stein, 1994).

Whether the effects of stress-induced increases in CRF and adrenal steroids on fetal growth and developmental timing are adaptive is a matter of debate. In humans, corticosteroid/fetal stress accelerates brain maturation and lung development, which would presumably enhance the viability of preterm infants (see Amiel-Tison, 2004). As in the case of larval amphibians facing a drying pond, it is hypothesized that early escape from a hostile fetal environment in mammals accelerates development such that the individual can transition to a terrestrial environment where resources may be more plentiful. As predicted by this hypothesis, in natural situations of multiple births where resources are assumed to be lower per fetus, the mean gestational length of triplets is shorter than twins, which is shorter than singletons (Alexander et al., 1998). The neurodevelopmental actions of thyroid and corticosteroid hormones may be the proximate link between environmental factors precipitating preterm birth and accelerated neurological development in humans. While the actions of CRF, thyroid hormone, and corticosteroids both promote preterm birth and

enhance immediate survival, studies of the long-term effects of elevated corticosteroids during gestation suggest that these early survival benefits come at a cost.

LONG-TERM PHENOTYPIC CONSEQUENCES OF EARLY LIFE STRESS

While accelerated metamorphosis increases the probability of survival, the resultant smaller size at transformation may be associated with future fitness costs. Both field and lab-based studies have shown that tadpoles reared in "hostile" environments metamorphose at a smaller body size, and the juveniles are thus more likely to exhibit slower growth rates, inferior locomotor abilities, greater susceptibility to starvation, and higher mortality (Altwegg and Reyer, 2003; Alvarez and Nicieza, 2002; Beck and Congdon, 1999, 2000; Berven, 1990; Goater, 1994; Relyea and Hoverman, 2003; Scott, 1994; Semlitsch et al., 1988; Van Buskirk and Saxer, 2001). In most species (but not all, see Beck and Congdon, 1999) this body size disadvantage at metamorphosis is retained through the age at first reproduction, thus compromising reproductive fitness (Altwegg and Reyer, 2003; Berven, 1990; Goater, 1994; Scott, 1994; Semlitsch et al., 1988). These studies demonstrate the importance of the tadpole environment for juvenile fitness; however, our understanding of how the larval environment causes these effects in later life stages is limited.

Interestingly, the effects of environmental stress on tadpole growth and development parallel those of intrauterine stress on fetal growth and development in mammals. Maternal malnutrition or repeated acute stress (e.g., shock, restraint) cause intrauterine growth retardation and preterm birth (Bloomfield et al., 2003; Challis et al., 2001; Weinstock et al., 1992, 1998), and both of these factors have been associated with reproductive dysfunction and increased susceptibility to disease later in life (Barker and Clark, 1997; Weinstock, 2001). These later-life effects of the in utero environment are associated with premature activation of the neuroendocrine stress axis in both mothers and fetuses (Matthews, 2002; Weinstock, 2001; Welberg and Seckl, 2001; Welberg et al., 2001). This activation, which causes an elevation in plasma glucocorticoids during critical windows of brain development, has been shown to permanently alter the functioning

of the stress axis and the expression of behaviors throughout the life of the animal. Because the structure and function of the neuroendocrine stress axis is largely conserved among vertebrates (Denver, 1999), it is likely that a similar mechanism may explain how tadpole environments affect juvenile phenotypic expression in amphibians.

Effects of pre- or neonatal stress on later HPA reactivity in mammals

Studies in mammals have shown that exposure to prenatal or neonatal stress alters the development of the HPA axis, thus causing altered function of physiological and behavioral stress responses later in life. Pre- or neonatal stress is typically associated with a "hyperresponsive" neuroendocrine stress axis, which consists of 1) elevated basal expression of hypothalamic CRF and plasma glucocorticoid concentration (McCormick et al., 1995; Meaney, 2001; Weinstock, 2001); 2) more fearful behaviors and anxiety (Meaney, 2001); 3) magnified or prolonged responses of CRF and cortisol to acute stressors (Lesage et al., 2004; Meaney, 2001); and 4) increased food intake associated with higher probabilities of obesity and metabolic dysfunction (Barker and Clark, 1997; Breier et al., 2001). These responses are complex, as they often depend on gender, the duration of exposure to stress, and the developmental stage when the stress was experienced (Matthews, 2002; Meaney, 2001). However, there is evidence that elevated maternal care and environmental enrichment can compensate for pre- or perinatal stress-induced effects (Caldji et al., 2000; Francis et al., 2002; Meaney, 2001).

The hyperreactivity of the neuroendocrine stress axis in mammals exposed to early life stress is associated with reduced glucocorticoid negative feedback, as shown by the simultaneous elevation in basal plasma cortisol concentration and CRF expression in the hypothalamus (paraventricular nucleus), prolonged elevations in plasma cortisol after a stress response, and reduced glucocorticoid receptor expression in the hippocampus (Meaney, 2001; Welberg and Seckl, 2001). In rodents, neonatal stress also alters CRF neuronal morphology in the paraventricular nucleus and other brain regions involved in the stress response (i.e., amygdala, hippocampus, and locus coeruleus; Meaney, 2001). We have mapped dense clusters of

CRF neurons in the same brain regions in the frog *Xenopus laevis* (Yao et al., 2004). The high conservation in expression patterns of CRF among tetrapod vertebrates suggests that the function of CRF circuits is also conserved (see also Lovejoy and Balment, 1999).

Studies in mammals suggest that the effects of pre- or neonatal stress on the development of the neuroendocrine stress axis results from the organizational actions of glucocorticoids on the brain (Weinstock, 2001; Welberg and Seckl, 2001; Welberg et al., 2001), similar to the well-known organizational actions of sex steroids (Simerly, 2002). Exogenous glucocorticoids increase the number of CRF neurons and reduce glucocorticoid receptor expression in mammals (Fujioka et al., 1999; Welberg and Seckl, 2001; Welberg et al., 2001). In many vertebrates, treatment with glucocorticoids during embryonic/fetal stages causes the same types of postnatal phenotypes as those seen following exposure to pre- or neonatal stress in mammals (Hayward and Wingfield, 2004; Jensen et al., 2002; Welberg and Seckl, 2001).

Effect of prenatal stress on food intake

An example of how exposure to corticosteroids during early development can affect later-life behavior and health is illustrated by the influence of reduced resources (i.e., maternal malnutrition) during fetal/larval stages on food intake behavior. In mammals, maternal nutritional stress causes increases in basal CRF content in the paraventricular nucleus and plasma corticosteroid concentration of the fetus/neonate, and is often associated with hyperphagia and "catch-up growth" (Breier et al., 2001; Vickers et al., 2000, 2003). Despite this compensation in body size, prenatally stressed individuals have higher probabilities of hypertension, obesity, and type II diabetes, among other diseases, during later life (Barker and Clark, 1997; Breier et al., 2001). Although the physiological mechanisms underlying catch-up growth are not yet understood, if pre- or neonatal stress programs basal plasma cortisol concentration to a higher "set point," then daily food intake is expected to be higher in these individuals given the orexigenic actions of glucocorticoids (Crespi and Denver, 2004a).

Similarly, reduced food availability or high conspecific density in the tadpole stage is

associated with increased food intake and compensatory growth in juvenile frogs, particularly in high food conditions (Morey and Reznick, 2001; Crespi and Denver, unpubl. data). Earlier, we found that food restriction increased whole-body corticosterone (the primary glucocorticoid in amphibians) content in tadpoles of the Western spadefoot toad (Crespi and Denver, 2004b), and central nervous system (CNS) regulation of food intake matures during early prometamorphic stages (Crespi and Denver, 2004a). Therefore, it is possible that increased exposure to corticosteroids during this time can affect the development of CNS feeding centers and thus permanently alter feeding behavior in later life stages. We are currently investigating the roles of CRF and corticosteroids in mediating the effects of the tadpole's environment on later life phenotypic expression to determine if these mechanisms are evolutionarily conserved.

CONCLUSIONS

The neuroendocrine stress axis represents a phylogenetically ancient signaling system that allows the fetus or larva to match its rate of development to the prevailing environmental conditions. In diverse vertebrate species, including humans, CRF and corticosteroids act both centrally and peripherally to alter the rate of development in response to unfavorable environmental conditions (Fig. 1). This neuroendocrine response generates life history transitions necessary for immediate survival. However, stress-induced acceleration of development may come at a cost, expressed as reduced fitness in the juvenile or adult stage. In humans, exposure of the fetus to elevated corticosteroids, either from the mother or the fetal adrenal gland, may predispose individuals to increased health risks throughout life. Thus, there are important trade-offs between immediate survival in the developmental habitat versus long-term phenotypic changes that result in reduced performance as an adult. These neuroendocrine/developmental responses, and their long-term phenotypic consequences, are deeply rooted in the evolutionary history of vertebrate animals, and future comparative studies will be invaluable to understanding the origins of human developmental plasticity.

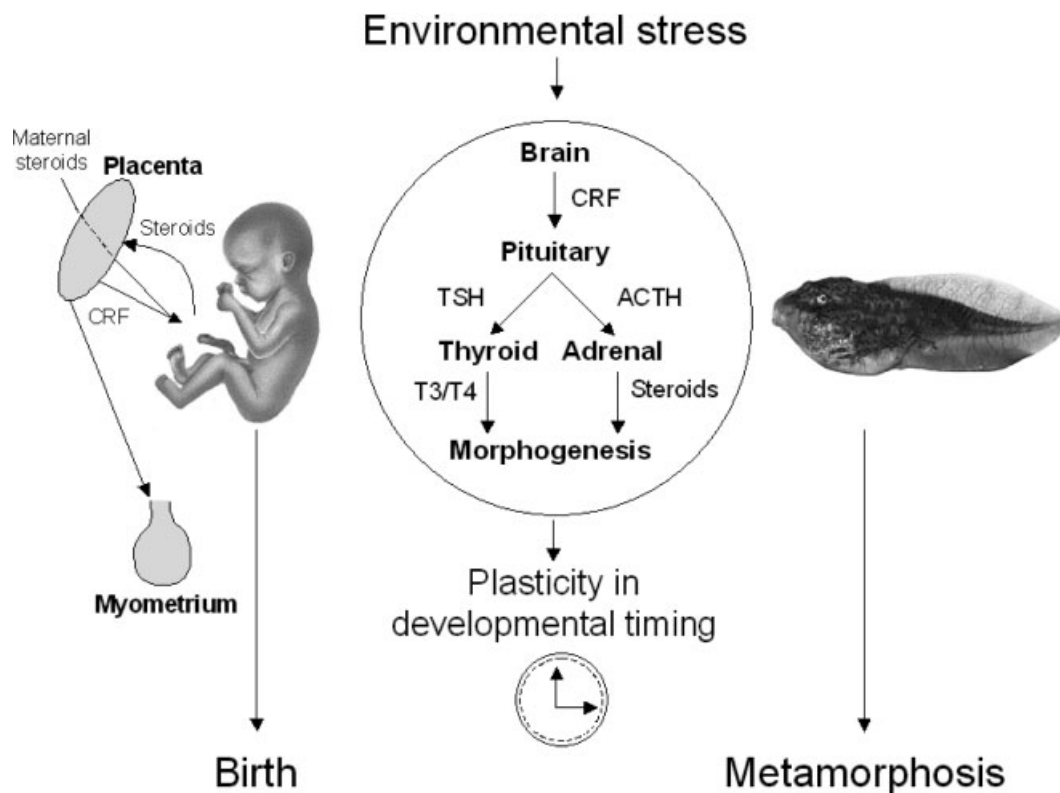


Fig. 1. Environmental conditions affect the timing of life history transitions through the evolutionarily conserved actions of stress hormones in humans and amphibians. Unlike the tadpole, which is a free-swimming animal, the human fetus is influenced by hormones of maternal and placental origin. Conversely, fetal hormones can alter physiology of the mother (and the placenta). For example, maternal cortisol is transferred to the fetal compartment and can alter fetal development. Adrenal steroids of fetal origin exert a positive feedback on placental CRF production and promote uterine contraction. Note that a role for CRF in the regulation of the human fetal thyroid gland has not been demonstrated. CRF, corticotropin-releasing factor; TSH, thyrotropin; ACTH, corticotropin; T3/T4, thyroid hormones.

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