

## Fetal adaptation to stress Part II. Evolutionary aspects; Stress-induced hippocampal damage; long-term effects on behavior; consequences on adult health

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### Abstract

Humans share adaptative capacities to stress with other species, as demonstrated on amphibians: the physiological response to experimental water volume and food deprivation results in the activation of the endocrine axes that drive metamorphosis, in particular the neuroendocrine stress system. Unfavorable effects may, however, occur, probably due to inappropriate timing and/or duration of stress: recent experiments are converging to show a profound impairment of hippocampal functioning in the offspring of mothers exposed to prenatal stress. Moreover, fetal changes are likely one of the risk factors for a number of diseases in adulthood.

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### 1. Evolutionary aspects of developmental acceleration

Modern humans are the product of over 1 billion years of organic evolution. While some traits that we possess are derived, many others have been conserved through

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evolution. By placing modern human structure and function in the context of our evolutionary history through the comparative study of diverse taxa, we can gain a better understanding of the origins of extant characters and their adaptive significance.

The range of possible organismal phenotypes is determined by the genotype and environment–genotype interactions. A single genotype can produce a variety of phenotypes in response to a changing environment and this phenomenon is often referred to as developmental or phenotypic plasticity [1]. Phenotypic plasticity in development allows organisms to develop either slowly or rapidly, depending on environmental conditions. Phenotypic plasticity refers generally to phenotypic variation induced by environmental change, and a plastic ‘reaction norm’, as described by Stearns [1], refers to the relationship between phenotypic variation and the environment when the phenotype varies as a continuous function of the environmental signal.

While a relatively fixed developmental period (gestational period) is thought to be the norm for humans and other endothermic animals, ectotherms (the ancestral vertebrate life history strategy) exhibit considerable variation in the timing of development owing to strong influences of the external environment. Embryonic development tends to be buffered against unpredictable environmental effects; that is, it is canalized. By contrast, postembryonic development tends to be more variable in its timing and susceptible to environmental influences. These environmental effects are often mediated by the regulated secretion, metabolism and action of hormones. The capacity to vary development in response to the environment likely arose very early in evolution.

### *1.1. Developmental plasticity: examples from amphibians*

The majority of amphibian species have complex life cycles. That is, after embryonic development and hatching, they remain in a larval stage for a period of time before undergoing a metamorphosis to the adult form. This is contrasted with the mode of development seen in mammals (and some amphibians) that lack a larval stage which is often termed ‘direct development’.

The length of the amphibian larval or premetamorphic period depends primarily on growth opportunities, and amphibians show extreme plasticity in the timing of metamorphosis that is directly related to conditions in the larval habitat. Water availability is arguably the single most important environmental variable for a tadpole. Amphibian species that breed in unpredictable habitats (e.g., arid habitats) show phenotypic plasticity in response to pond drying [2]. Denver et al. [3] manipulated water levels in aquaria in which tadpoles were reared and showed that tadpoles accelerate metamorphosis as the water volume is reduced. Tadpoles can grade their developmental response with respect to the rate of water volume reduction. Similarly, metamorphosis can be accelerated by food restriction. The physiological response to experimental water volume and food deprivation results in the activation of the endocrine axes that drive metamorphosis (Ref. [4]; see below).

The diverse morphological and physiological changes that occur during metamorphosis are orchestrated by hormones as first demonstrated by Gudernatsch [5] who showed that the vertebrate thyroid gland contained a factor that could induce precocious metamorphosis if fed to tadpoles. Thyroid hormone (TH) is now known to be the primary hormone

controlling amphibian metamorphosis [2]. In vertebrates, TH can act as both a developmental switch (as in the case of amphibian metamorphosis) and as a maturational factor. Thyroid hormone plays an essential role in the maturation of the vertebrate CNS [6–8]. In humans, the deleterious effects of  $T_3$  deficiency on neural development (i.e., cretinism) have been known for centuries. The lack of  $T_3$  during fetal life in mammals results in abnormal axonal and dendritic development, synapse formation, cell proliferation and myelination [7,8]. Despite the seemingly profound differences in development between metamorphosing amphibians and direct developing species (e.g. mammals), recent findings demonstrate the deep evolutionary conservation of basic molecular and cellular processes in development [9–11].

### *1.2. Developmental thresholds for accelerated metamorphosis*

There appears to be a minimum body size for metamorphosis that differs for each species [12]. This minimum body size is likely to be correlated with a level of development of the tadpole's endocrine system to support the production of hormones necessary for metamorphosis. The tadpole's neuroendocrine system (hypothalamus, median eminence and pituitary) develops in response to rising plasma titers of thyroid hormone that occurs during metamorphosis. Once the neuroendocrine system develops the animal is capable of making developmental 'decisions' in response to changing environmental variables [2]. That is, if conditions are favorable in the larval habitat, hormone production remains low and tadpoles continue to capitalize on favorable growth conditions. However, after a certain body size/stage of development is attained, if environmental conditions deteriorate, tadpoles have the capacity to activate endocrine systems and transition from the larval to the adult habitat where growth opportunities might be more favorable.

For example, tadpoles can accelerate metamorphosis in response to pond drying or food deprivation only after they reach a stage of development at which they become competent to respond. Before this stage is attained growth and development is inhibited. Although this threshold developmental stage has not been analyzed systematically and may vary among species, it probably corresponds to the stage at which the hypothalamus and median eminence mature, thus allowing for the transfer of neurohormonal signals to the pituitary gland [2,13].

### *1.3. The vertebrate neuroendocrine stress system and its role in orchestrating life history transitions*

Mounting evidence from diverse animal species suggests that the neuroendocrine stress axis integrates sensory input regarding habitat quality and translates this information into a developmental response [2–4,14–22]. Developmental plasticity mediated by hormones is exemplified by the finding that stress hormones can function as important modulators of amphibian development, and may serve as a developmental 'switch' [18], allowing animals to match their phenotype to the prevailing environmental conditions. Tadpoles can accelerate their development when their habitat deteriorates (i.e., when conditions

become ‘stressful’), metamorphosing into small frogs at an earlier age and thus escaping mortality in the larval habitat (Fig. 1).

The production of thyroid hormone, the primary metamorphic hormone, is controlled by pituitary thyrotropin (TSH) which in turn is controlled by hypothalamic releasing factors. Other hormones, particularly the corticosteroid (CS) hormones, are known to

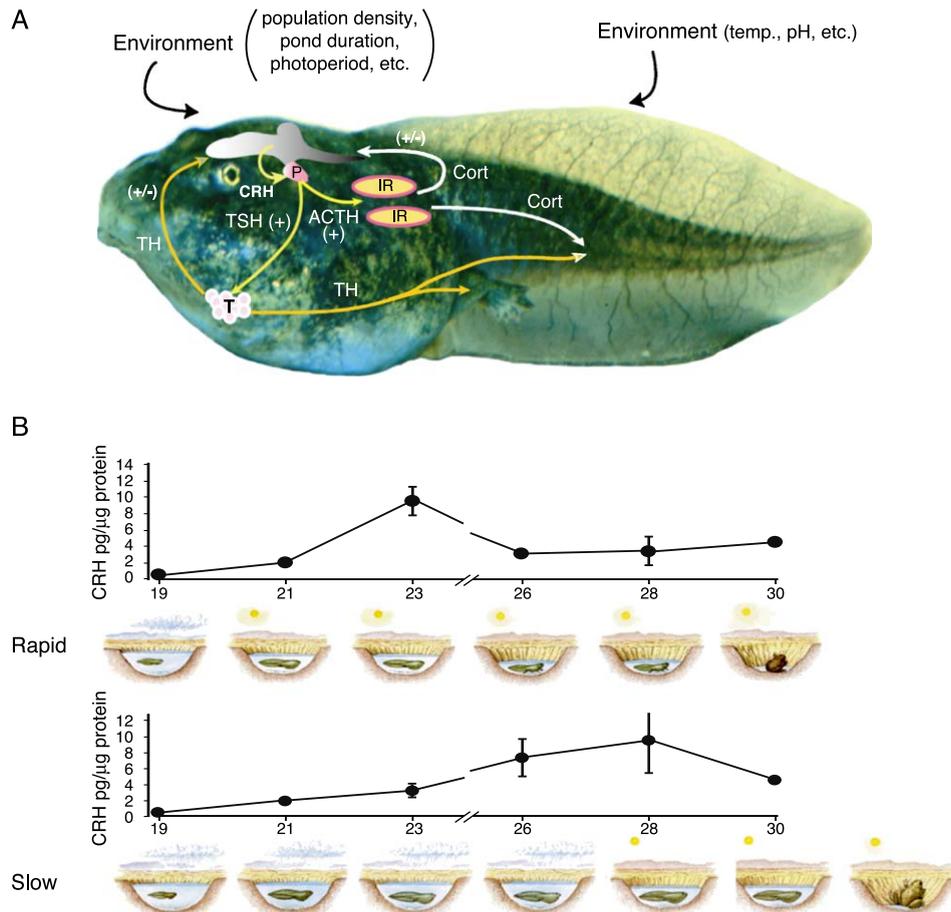


Fig. 1. (A) Endocrine systems controlling tadpole metamorphosis. P—pituitary gland; CRH—corticotropin-releasing hormone; IR—interrenal gland; ACTH—adrenocorticotrophic hormone; TSH—thyroid stimulating hormone; T—thyroid gland; TH—thyroid hormone; Cort—corticoids. Pluses indicate a stimulatory effect and minuses 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. CRH stimulates secretion of both TSH and ACTH, thus simultaneously up-regulating the thyroid and interrenal (adrenal) axes. Modified from Seasholtz et al. [44]. (B) Hypothalamic CRH peptide content increases precociously in Western spadefoot toad tadpoles exposed to simulated pond drying. The CRH data are modified from Denver [15]. Pictures under the graphs illustrate the acceleration of tadpole metamorphosis in response to rapid pond drying (vs. slow pond drying). Modified from (Scientific American).

influence thyroid hormone action (see Ref. [23]). The production of CSs is controlled by pituitary adrenocorticotrophic hormone (ACTH) which is in turn controlled by hypothalamic releasing factors. It has long been known that the hypothalamus is necessary for metamorphosis [13].

Importantly, the production of both TH and corticosteroids is controlled by a common neuroendocrine stress pathway in tadpoles and other nonmammalian species, which has led to the hypothesis that stressful environmental conditions accelerate tadpole development through the precocious activation of the thyroid and adrenal (interrenal) glands [24]. The hypothalamo-pituitary-adrenal (HPA) axis plays an essential role in mediating an animal's response to its environment, and its activation can have profound fitness consequences [25]. Circulating CS concentrations are elevated in many taxa in response to environmental stress (i.e., food deprivation, extreme weather, exercise, crowding, among others; [26–30]). Corticosteroids increase metabolic rate and mobilize fuel stores, a response thought to enhance performance during emergency or stressful events [26].

Most studies of the activation of the stress axis, and the physiological actions of CSs have focused on the adult stage. However, stress hormones play important roles during development. The stress axis, acting both centrally and peripherally, can transduce environmental signals into developmental responses. In tadpoles, TH controls metamorphosis and CSs synergize with  $T_3$  to accelerate metamorphosis [23]. A recent analysis of the molecular basis for this synergy showed that CSs up-regulate thyroid hormone receptors (TRs) in tadpole tail at the transcriptional level [31]. In addition, type II monodeiodinase gene expression is synergistically regulated by TH and CS, which can generate the biologically active form of TH, 3,5,3' -triiodothyronine ( $T_3$ ), from thyroxine ( $T_4$ ) within target tissues [31,32]. 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 can accelerate tadpole metamorphosis (all of which elevate CSs; [2]).

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) [13]. The importance of hypothalamic control of metamorphosis has long been recognized [13,23]. 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 [13,23]. Considerable evidence now supports a role for CRH as a larval amphibian TRF and controller of metamorphosis [14]. CRH is a 41-amino-acid polypeptide first isolated for its ability to stimulate ACTH secretion in mammals [33,34]. Numerous studies have shown CRH to be a potent TRF in non-mammalian species including tadpoles [14,35–40]. CRH accelerates metamorphosis through its combined actions on  $T_3$  and CS production [15,17,18,41,42]. Thus, the thyroid and the HPA axes can interact at both central and peripheral levels to influence the timing of metamorphosis [2].

Simulated pond drying or handling stress (handling, shaking, injection) activates both the HPA and thyroid axes in tadpoles [15,21]. It is noteworthy that handling stress in neonatal rats increases thyroid secretion. Meaney et al. [43] recently showed that handling

stress-induced glucocorticoid receptor (GR) expression in hippocampus of neonatal rats depends on this increase in  $T_3$ . These findings provide further evidence for a linkage between the thyroid and HPA axes in developing animals, and highlight the importance of comparative studies for understanding the role that such relationships play in vertebrate development.

The neuroendocrine stress system, with CRH as the primary player, may represent a phylogenetically ancient modulator of developmental timing through its regulation of adrenal and thyroid gland secretion [14]. For these reasons, activation of the neuroendocrine stress system likely plays an important role in development in diverse vertebrate species including humans [40]. 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.

## 2. Stress-induced hippocampal damage

Results of recent experiments are converging to show a profound impairment of hippocampal functioning in the offspring of mothers exposed to prenatal stress. For example, when dexamethasone is injected into pregnant rhesus macaques, cell counts in the hippocampus showed decreased numbers of neurones in the CA region and dentate gyrus [45]. Effects of stressed-induced corticosterone secretion have been studied also in male rats [46]: a decrease in type I hippocampal corticosteroid receptors and an increase in glucocorticoid secretion have been observed. These effects are blocked if stress-induced glucocorticoid secretion is suppressed by adrenalectomy in the mother and observed if substitutive corticosterone is administered during stress in these mothers. Along with these observations, it has also been shown that prenatal stress decreases synaptic density in the CA3 area, the projection site of the granule neurons [47] in the dentate gyrus of the hippocampus, and hippocampal density of nitric oxide producing neurons [48].

More recently, a negative effect of prenatal stress has been identified as one of the unique features of the hippocampal formation, i.e. the production of new neurons in the dentate gyrus of the hippocampus that is observed throughout the entire life span of the individual [49–51]. This phenomenon named neurogenesis has recently attracted a great deal of attention in the scientific community and has been implicated in hippocampal-mediated learning [50,51]. Offspring of prenatally stressed mothers show decreased neurogenesis throughout their development, including adult life and aging [52]. Furthermore, the increase in neurogenesis induced by learning in control individuals is absent in adult prenatally stressed rats [52].

This diminished hippocampal function, as a consequence of prenatal stress, is in agreement with the increased corticosterone secretion and alteration of glucocorticoid circadian rhythmicity repeatedly observed in prenatally stressed subjects during development [53] and adulthood [54–56]. Thus, the hippocampal formation is one of the major structures involved in the negative feedback control of glucocorticoid secretion [57–61].

It is important to notice, however, that such an increase in glucocorticoid secretion could be the result of impaired hippocampal function or the cause of it. Thus, an increase in glucocorticoid levels has been shown to have a negative influence on neurogenesis in

the adult [62–64] and induces an impairment of hippocampal function and learning ability during aging [65–68]. The possibility of a primitive deregulation of glucocorticoid secretion in prenatally stressed animals is suggested by the observation that an increase in glucocorticoid secretion precedes the loss in hippocampal corticosteroid receptors observed in these subjects [53]. Recent experiments on these issues are reviewed by Mc Ewen [69] under the title of «stress and hippocampal plasticity» and by Matthews [70] concerning antenatal glucocorticoids and programming of the developing brain.

### 3. Long-term effects on adult behavior

Several studies have investigated the effects of prenatal stress on the behavioral performance of rodents. Two major behavioral domains have been investigated: (a) the appearance of learning disabilities, and (b) the propensity to develop drug abuse. In both cases, a negative effect of prenatal stress has been found. Thus, prenatally stressed subjects have a lower performance in hippocampal-mediated learning tasks and this especially during aging [52–71]. In parallel, prenatally stressed rats have a higher propensity to develop self-administration of drugs of abuse [72] and show a higher levels of drug-induced adaptations involved in the development of drug dependence [73,74]. As a corollary of these modifications an altered behavioral and endocrinological response to novelty and stressful environments has also been observed in the offspring of stressed mothers [75–78]. This suggests a more general impairment of the capability of the subject to cope with external challenges.

In general, these adverse effects of prenatal stress have been attributed to the increased glucocorticoid secretion observed in such offsprings [79]. Thus, increased levels of these hormones have been shown to impair hippocampal plasticity and accelerate loss of memory during aging [65–68], as well as to increase the propensity to self-administer drugs of abuse in adult rats [80].

In agreement with this research in animals, data from retrospective studies on children whose mothers experienced psychological stress or adverse life events during pregnancy suggest long-term neurodevelopmental effects on the infant [81–84]. Several disturbances in child development and behavior have been described, ranging from unsociable and inconsiderate behaviors, hyperactivity-attentional deficit disorder and sleep disturbances, to some psychiatric disorders including schizophrenic episodes, depressive and neurotic symptoms, drug abuse, mood and anxiety [81,85–91]. Furthermore, mother's stress or anxiety seems linked with prematurity or low birthweight [92–94], as well as a lower blood circulation in the fetal middle cerebral artery that can affect fetal brain development [95]. Prenatal stress also significantly worsened the scores on the neonatal neurological examination [96] and was associated with subsequent increased HPA axis responsiveness reminiscent of major depression in adults [97].

It is important to notice in this context that if research in animals suggests that prenatal stress has negative effects on health and behavior, it also suggests that these modifications are not irreversible. Thus, it has been shown with several approaches that manipulations augmenting maternal behavior can reverse the effect of prenatal stress [77,71]. In particular, somatosensory stimulation of the pup by the mother seems to play an important

role. A better understanding of the molecular and cellular basis of these effects will probably lead to the development of therapeutic interventions that could counteract the effects of prenatal stress.

#### 4. Consequences on adult health

Until recently, school difficulties and their long-term negative effects on adult life have been the main concern about IUGR neonates [98]. In the nineties, a new field of investigations opened, when Barker and Osmond [99] and Barker et al. [100] suggested long-term effects of fetal undernutrition on the occurrence of chronic adult diseases, based on the findings from historical cohort studies in UK. Their first results show a correlation between neonatal mortality in 1920 and mortality due to cardiovascular diseases 50 to 70 years later. Individual studies correlating growth parameters at birth and mortality due to cardiovascular diseases in adulthood have been developed [101,102]. Based on these results, Barker [103] therefore suggests the hypothesis that chronic adult diseases are programmed in utero: Adaptation to malnutrition should have definitive effects on metabolism and organ structure that determine the occurrence of coronary heart diseases, hypertension and diabetes in adulthood.

Such a long-term effect of in utero circumstances appeared revolutionary in 1993, so surprising that the question of potential selection bias was raised. Numerous other studies have been performed in various countries, confirming the association between low birthweight and adult chronic diseases. Underlying mechanisms, however, are poorly understood. Other types of explanation have been proposed after the Barker hypothesis including genetic factors [104].

Studies on twins with discordant birthweight [105] show a higher adult mortality in smaller twins compared to larger, thus favoring the Barker's hypothesis. The study of Christensen et al. [106] in twins also demonstrates the contribution of genetic factors, though modulated by environmental circumstances.

For the time being, fetal programming of adult health is generally accepted [107]. However, many questions remain: Is there a critical period? Is there a threshold? Or is it a response with different degrees including no pathologic effects? What is the effect of postnatal life, i.e. are factors after birth able to increase or decrease the tendency dictated by fetal environment and/or genetic factors? More animal studies are in process, such as the one of Olivier et al. [108] on sheep. The hope of new interventions on newborn infants at risk is implicit in these studies [109].

Trying to provide a less stressful environment postnatally works in this direction, under the name of Developmental Care: repeated stress being part of the everyday life of VLBW infants in NICUs, it is very likely beneficial to reduce additional stress for infants who already experienced an abnormal pregnancy. Efforts to reduce postnatal stress have been initiated by Als and Gilkerson [110] by continuous adjustment of the level and nature of external stimuli to the developmental stage of the infant. The goal is to promote neuronal as well as glial cell growth, multiplication and migration, selection and differentiation of the neuronal network, as reviewed elsewhere [111,112]. Preliminary data obtained by quantitative magnetic resonance imaging of brain development in VLBW infants receiving

Individualised Developmental Care compared to controls are in favor of those stress-reducing interventions [113].

## 5. Conclusion

Adaptation to an unfavorable environment appears to be a life-saving answer, as demonstrated in desert amphibians: tadpoles of these species can accelerate metamorphosis as their pond dries, with earlier birth of a more mature product, as long as an unfavorable larval environment is not experienced too early or too severely. Similar adaptive phenomena are observed in humans when fetal adverse circumstances are not too early or too severe. Mechanisms are grossly similar, with a stress-induced elevation of corticosteroid secretion.

However, there is very likely a price to pay for this immediate beneficial effect on survival. Hippocampal damage could explain the high rate of learning disabilities in these high-risk pregnancies, mentioned for decades in the follow up literature. More recently, an altered biology for a lifetime has been studied: fetal changes are likely one of the risk factors for a number of diseases in adulthood. The new goals of preventive medicine will be to investigate prenatal strategies to optimize fetal programming.

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