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Commentary

Lessons From Tadpoles on the Physiological Roles of Corticosteroids

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Abbreviations: ACTH, adrenocorticotropin hormone; CRH, corticotropin-releasing hormone; GR, glucocorticoid receptor; MR, mineralocorticoid receptor; POMC, proopiomelanocortin; TH, thyroid hormone; TRH, thyrotropin-releasing hormone; TSH, thyrotropin (thyroid-stimulating hormone).

Stress and Metamorphosis

The primary hormone that drives developmental change during amphibian metamorphosis is thyroid hormone (TH), although metamorphic timing is ultimately controlled by the hypothalamus. So, which hypothalamic neuropeptide induces metamorphosis? Like most endocrinologists, you probably just guessed "thyrotropin-releasing hormone" (TRH), and if so, let me be the first to forgive you for this incorrect choice. The right answer, in fact, appears to be corticotropin-releasing hormone (CRH), the hypothalamic release factor that stimulates the secretion of adrenocorticotropic hormone (ACTH) from the adenohypophysis, functioning at the top of the hypothalamic-pituitary-adrenal stress axis in all vertebrates. Classic studies by Robert Denver and colleagues (1) have shown that whereas injections of TRH into tadpoles neither stimulates TH synthesis nor accelerates metamorphosis, injection of CRH induces pituitary thyroid-stimulating hormone (TSH) secretion, promoting TH synthesis and earlier metamorphosis. Therefore, in contrast with the conventional model of hypothalamic-pituitary-thyroid regulation with TRH at the top of the axis, in tadpoles CRH exerts dual functions, simultaneously stimulating both ACTH and TSH and inducing the adrenocortical and thyroid pathways, respectively. CRH has since been shown to stimulate TSH synthesis in fish, salamanders, and chickens, and hormones of the stress axis are also implicated in modulating the timing of birth in humans and other mammals.

Glucocorticoids and Thyroid Hormones: A Synergistic Relationship

Although TH is required to initiate virtually all of the diverse developmental programs of amphibian metamorphosis, the transformation cannot be completed in the absence of glucocorticoids produced by the interrenal glands (in frogs and fish the adrenal gland is called the *interrenal* gland). Indeed, death occurs in metamorphosing tadpoles lacking the gene for either proopiomelanocortin (POMC, the precursor to ACTH) or the gene for glucocorticoid receptor (GR) (2-4). However, although treatments of these mutant tadpoles with TH rescue them from death, considering that in both mutants some corticosteroid signaling through the mineralocorticoid receptor (MR) is still feasible, the authors of the studies did not rule out the possibility of vital roles for corticosteroids in metamorphosis that are independent of TH signaling. Among tetrapods, the most active mineralocorticoids are aldosterone and 11-deoxycorticosterone (DOC). Importantly, glucocorticoids bind to MR with similar affinity as mineralocorticoids, and as such are biologically active ligands of MRs. By contrast, mineralocorticoids have relatively low affinity to GRs. Among most vertebrates, the primary glucocorticoids are hydrocortisone/cortisol (most abundant in fish and in many larger mammals), and corticosterone (most active in amphibians, reptiles, and birds, as well as smaller mammals).

In order to gain further insight into the importance of corticosteroid signaling in amphibian metamorphosis, Bidisha and colleagues (5) created 21-hydroxylase (cyp21a2) knockout *Xenopus tropicalis* frogs. Since the cyp21a2 enzyme is essential for the synthesis of both corticosterone and aldosterone, the researchers reasonably expected that lack of signaling by both corticosteroids would result in an even more severe phenotype than those previously observed in GR and POMC knockout tadpoles. Much to the authors' collective surprise, although development to and through metamorphosis was delayed, unlike the GR and POMC mutants the cyp21a2 knockouts managed to somehow survive metamorphosis and live to adulthood. What accounts for the unanticipated reduction of phenotype severity? The authors postulate that, in contrast with the other mutants, the cyp21a2 knockouts may survive metamorphosis by either having higher plasma TH and/or supplementing low corticosterone production with a combination of other corticosteroids and corticosteroid precursors to sufficiently activate the glucocorticoid receptor and increase TH signaling. Potential glucocorticoid candidates include cortisol, which

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did not change in the cyp21a2 tadpoles and was double the concentration of that of the POMC mutants. Another possible source of GR signaling involves progesterone, which is known to transactivate the GR in mammalian systems, and increases ~30-fold in cyp21a2 mutants.

This study highlights the notion that GR transactivation by a collective compensatory assortment of weaker ligands may produce physiological effects comparable to that of a single primary ligand. The tractability and speed of this amphibian model sets the stage for future studies using POMC-cyp21a2 double knockout mutants to examine varying concentrations and combinations of corticosteroid precursors and/or new pharmacological compounds for their potential to rescue the double mutants in vivo. More generally, this study also demonstrates that the use of knockout models in *Xenopus*, like the cyp21a2, GR, or MR, are powerful tools for understanding these signaling pathways and the redundancy of adrenocorticosteroids in vertebrate early development.

Applications to Ecology and Medicine

The notion that glucocorticoids can potentiate the effects of a developmental morphogen, TH, integrates well with ecological models postulating that stressful changes in environmental parameters, such as reduced food availability, evaporating water levels, increased conspecific density, or increased predation, may promote metamorphosis. Considering that amphibians constitute the world's most threatened group of vertebrates, the cyp21a2 model could be used to enhance understanding of how corticosteroids respond to environmental stressors like the emerging threat of anthropogenic salinification of freshwater systems (6) or how these hormones influence energy balance and immune function when facing infectious disease in combination with environmental stressors (7). Beyond amphibian metamorphosis, glucocorticoids have been shown be key modulators of developmental plasticity and life history transitions across vertebrates, ranging from hatching in birds to the timing of birth in humans (1, 8).

Amphibian metamorphosis is not just a fascinating developmental phenomenon in its own right, but its ontogenetic and endocrine parallels to human perinatal development are uncanny. In each case, the organism abruptly switches from an aquatic environment to an air-breathing one. Shared physiological changes that accompany this transition include development of virtually every organ system, including the lungs, kidneys, gut, brain, and skeletal system. Even more intriguing is that all of these postembryonic developmental events are regulated by the same hormones in both animals, with TH and glucocorticoids peaking at birth and metamorphosis, and each playing prominent roles in organ development. Considering the conservation of TH and corticosteroid functions between frogs and humans, information gained from the tractable frog model will continue to provide fundamental insights that further our understanding of endocrine diseases and disruptions to human development.

Disclosures

The author has no potential conflicts of interest.

Data Availability

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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