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2 **The chicken and egg situation of thyroid hormone and glucocorticoid signaling during post-**
3 **embryonic development.**

4

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6

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20

21 Post-embryonic development refers to the period of development after
22 embryogenesis. This normally includes extensive growth, patterning and morphogenesis. In
23 mammals including human, the perinatal period is marked by post-embryonic development
24 regulated by a hormonal tsunami. Indeed, multiple hormones regulate fetal growth, brain
25 development and organ maturation in preparation for extra-uterine life.

26
27 Two types of these hormones, thyroid hormones (THs) and glucocorticoids (GCs) play
28 prominent and widespread roles during this period. They share common key-target regions
29 (hypothalamus and pituitary) for the control of other hormone synthesis. They regulate
30 common and specific processes, and interact at multiple levels to affect their targeted
31 physiological processes. Their actions are mediated by ligand-activated transcription factors,
32 which are members of the nuclear receptor superfamily and therefore have structural
33 functional similarity. Genetic and environmental perturbations of TH and/or GC signaling may
34 cause morphological and physiological impairments. These disruptions may also predispose
35 individuals to diseases of adulthood, including neurologic, metabolic and cardiovascular
36 diseases. All these significant health consequences motivate efforts to look for treatment
37 options to avoid or mitigate potential pathologies. Unfortunately, endocrine and molecular
38 mechanisms pertinent to the perinatal period are not well elucidated. In order to understand
39 mechanisms in developmental endocrinology, animal models are required. Since such
40 physiological processes are difficult to study in uterus-enclosed mammalian embryos,
41 especially due to confounding maternal effects, alternative models can be attractive. The
42 Anuran amphibian model is a pertinent choice. In this issue of *Endocrinology*, the manuscript
43 from Shewade et al. (1) presents elegant work that manages to address in amphibian the
44 question of the interaction between TH and GCs signaling during post-embryonic
45 development.

46
47 As for birth in mammals, larval metamorphosis which occurs in anuran amphibians and
48 some fish, represents a remarkable post embryonic developmental crisis. Frogs and humans
49 have THs and GCs which peak at metamorphosis and birth, respectively, have comparable
50 roles for these hormones in many target organs, have conserved hormone receptors and
51 mechanisms of gene regulation. In addition to highly conserved regulations, roles and action
52 mechanisms of THs and GCs, frog is also a valuable vertebrate model because metamorphosis
53 in their post-embryonic developmental period is independent of maternal endocrine
54 influence. Amphibian metamorphosis is an ecological life transition accompanied by
55 spectacular morphological, physiological and behavioral changes (such as diet, locomotor
56 organs, respiratory system, etc.). Investigations by various authors revealed that the
57 concerted responses to THs in different tissues towards sometimes opposite fates: apoptosis
58 (e.g., resorption of the tail or the gills), proliferation (e.g., limb morphogenesis), and
59 remodeling (e.g., the intestines or the central nervous system) require GCs (2). In amphibians
60 as in all vertebrates, GCs are also key regulators of intermediary metabolism, and the well-
61 known mediators of the stress response playing the role of interface with environmental
62 signals. In Anuran amphibians, GCs increase THs signaling to accelerate metamorphic
63 progression and allow escape from an unfriendly environment. Last but not least,
64 metamorphosis corresponds to the transition from an aquatic environment to air breathing,
65 that can be seen as a reminiscent of emergence onto land of tetrapod ancestors, and be also
66 compared to the transition from foetal life in amniotic liquid to first air breathing of the new-
67 born.

68 Since the past few years, TALEN or CRISPR-Cas gene knock out methodologies have
69 been applied to decipher the specific roles played out by THs receptors, TR alpha and beta, in
70 the regulation of the various metamorphic processes in *Xenopus tropicalis* (3, 4). To address
71 the requirement for GCs in metamorphosis, TALEN knock out of GCs receptor (GR) was
72 recently performed, and revealed that GR is necessary for survival of *Xenopus tropicalis*
73 throughout metamorphosis (5). In the work presented by the same group, Shewade et al. (1)
74 further investigated the role of GCs, by using TALEN gene disruption to knock out *pomc*
75 (proopiomelanocortin) gene in *Xenopus tropicalis*. The *pomc* gene encodes a polypeptide
76 hormone precursor, itself not functional, but that undergoes extensive tissue-specific post-
77 translational modification to generate a range of smaller biologically active peptides. In
78 corticotroph cells of the anterior pituitary, the cleavage of the pro-peptide leads to one of the
79 major end products, the adrenocorticotrophin (ACTH). ACTH is involved in the stimulation of
80 the adrenal gland and in the cortical secretion of GCs. Shewade et al. made use of this property
81 to prevent GCs production by knocking out the *pomc* gene. As expected, mutant tadpoles have
82 a reduced plasma corticosterone level at metamorphosis. These tadpoles have also reduced
83 expression of GCs-response genes and TH-response genes. Importantly, their rates of growth
84 and development is reduced with death inevitably occurring towards the end of
85 metamorphosis during tail resorption. The death of *pomc* KO mutants, like the GR KO mutants,
86 further supports the critical role of GCs for survival through frog metamorphosis. Death can
87 be prevented by exogenous corticosterone treatment but also by THs treatment. This ability
88 of exogenous THs to overcome death in *pomc* mutants by itself indicates a strong interaction
89 between the two hormones to ensure the completion of all transformations through
90 metamorphosis. However, the physiological reasons of the death in GR or *pomc* KO mutants
91 still remain to be addressed, as many hypotheses could be advanced, such as insufficient
92 development of crucial organs (i.e. maturation of the lungs, a critical step at birth in human),
93 dyssynchrony of organs/tissues transformation during metamorphosis, or shortage in
94 metabolites and energy supplies highly essential through metamorphosis.

95 In human, as in frogs, POMC-deficiency results in hypo-cortisolism. At human birth, if
96 untreated, it leads to death mainly as a consequence of lung immaturity. In premature infants,
97 to remedy ineffective pulmonary function, prenatal GC administration is routinely used to
98 accelerate lung maturation. Obesity, adrenal insufficiency and red hair are the phenotypes
99 found when the *pomc* gene is affected in humans (6). In mouse, homozygote deficiency of
100 *pomc* gene is associated with obesity, increased food intake, adiposity, defects in adrenal
101 development, and altered pigmentation (7). Serum corticosterone are below detectable
102 levels. However, unlike frogs, lack of all derived POMC peptides is compatible with some
103 survival throughout prenatal development, with still partial embryonic lethality associated
104 with POMC deficiency. More interesting, the *pomc* *-/-* mice show lowered serum levels of
105 thyroxine (8), implicating central melanocortin signaling in the regulation of the hypothalamic-
106 pituitary-thyroidal axis. Unfortunately, Shewade et al. do not contribute information on the
107 issue of GCs actions on the hypothalamic-pituitary-thyroidal axis and THs production. Their
108 surprising result showing that supplementation with THs allows the *pomc* knock-out tadpoles
109 to survive suggests that GCs act on the state of thyroid axis or signaling.

110
111 It seems that THs and GCs can regulate each other depending on molecular, cellular and
112 physiological context. This cross-regulation can amplify hormone signals, regulate hormone
113 activities, and coordinate hormone actions. In line with their crosstalk and synergism in the

114 regulation of crucial steps of post-embryonic development, a concomitant rise in THs and GCs
115 is observed during perinatal/post-embryonic period in mammals, hatching in birds and
116 reptiles, as well as fish and amphibian metamorphosis. The cross-talk acts on different steps
117 of the THs and GCs signaling pathways. At the level of the hypothalamus and pituitary, it
118 involves corticotropin releasing hormone (CRH) itself, which in fish, amphibians, reptiles and
119 birds, stimulates not only the release of ACTH as in all vertebrates, but also that of thyroid-
120 stimulating hormone (TSH), a regulation that might have been lost in mammals. At central and
121 peripheral levels, when GCs synergize with THs to accelerate tadpole metamorphosis, GCs
122 increase TR binding capacity, increase conversion of active THs from pro-hormone, and
123 decrease the degradation of THs. GCs treatment also upregulate TR expression. Conversely,
124 THs are involved in GCs receptor regulation, increasing or decreasing expression depending
125 on the studied tissues. The situation is therefore similar to the chicken or the egg causality
126 dilemma with the difficulty of sequencing actions where each seems to depend on others
127 being done first. It seems that TH acts before GC and vice versa, that TH controls GC synthesis
128 and vice versa, as well as TH action controls GC action and vice versa. All these interactions /
129 modes of regulation deserve to be researched in mammals.

130

131 While focus has traditionally been put on the role of THs in amphibian metamorphosis,
132 these new advances highlight the role of GCs and the cross-talk with THs. Involvement of GCs
133 and THs cross-talk appears as a common feature to fish and amphibian metamorphosis, bird
134 hatching and mammal birth. This suggests that THs and CGs interaction in the regulation of
135 postembryonic developmental crisis, has an ancient origin and has been largely conserved
136 throughout vertebrate evolution. From an evolutionary and adaptative perspective, the
137 corticotropic stress axis with GCs, may be the best candidate to have first linked
138 environmental cues to triggering of metamorphosis and change of ecophase, in vertebrates.
139 On the other side, the major role of the thyrotropic axis in the regulation of development in
140 vertebrates may lead to the opposite hypothesis. In extant species, the current knowledge
141 does not allow either to clearly define the temporal sequence of THs and GCs actions and
142 interactions in the regulation of post-embryonic development, a dilemma similar to the
143 chicken and egg metaphor.

144

145 This being said, these observations come with a lot of new challenges and questions to
146 fully understand the respective role of THs and GCs and their cross-talk during post-embryonic
147 period, that can be addressed with relevant non-mammalian models, opening new research
148 perspectives to potentially avoid or mitigate health consequences of disturbed THs or GCs
149 signaling.

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