General and Comparative Endocrinology 228 (2016) 60–68

Contents lists available at ScienceDirect

General and Comparative Endocrinology

journal homepage: www.elsevier.com/locate/ygcen

Review article

Corticotropin-releasing hormone: Mediator of vertebrate life stage transitions?

Yugo Watanabe, Sylvia V.H. Grommen, Bert De Groef*

Department of Anatomy, Physiology and Microbiology, La Trobe University, Bundoora, Victoria 3086, Australia

ARTICLE INFO

Article history:
Received 1 November 2015
Revised 7 February 2016
Accepted 9 February 2016
Available online 10 February 2016

Keywords:
Corticosteroid
Corticotropin-releasing hormone
Metamorphosis
Thyroid hormone
Thyrotropin
Vertebrate life stage transition

ABSTRACT

Hormones, particularly thyroid hormones and corticosteroids, play critical roles in vertebrate life stage transitions such as amphibian metamorphosis, hatching in precocial birds, and smoltification in salmonids. Since they synergistically regulate several metabolic and developmental processes that accompany vertebrate life stage transitions, the existence of extensive cross-communication between the adrenal/interrenal and thyroidal axes is not surprising. Synergies of corticosteroids and thyroid hormones are based on effects at the level of tissue hormone sensitivity and gene regulation. In addition, in representative nonmammalian vertebrates, corticotropin-releasing hormone (CRH) stimulates hypophyseal thyrotropin secretion, and thus functions as a common regulator of both the adrenal/interrenal and thyroidal axes to release corticosteroids and thyroid hormones. The dual function of CRH has been speculated to control or affect the timing of vertebrate life history transitions across taxa. After a brief overview of recent insights in the molecular mechanisms behind the synergic actions of thyroid hormones and corticosteroids during life stage transitions, this review examines the evidence for a possible role of CRH in controlling vertebrate life stage transitions.

Contents

1. Introduction

Life stage transitions are central events in the life cycles of many vertebrate species. During the transition, animals often undergo morphological, physiological and behavioral transformations associated with complex hormonal activity. A remarkable commonality between vertebrate life stage transitions as diverse as salmonid smoltification, amphibian metamorphosis, hatching in precocial birds, and birth in precocial mammals, is that these processes are all accompanied by increases in both circulating thyroid hormones and corticosteroids (*e.g.*, Björnsson et al., 2011; Brown and Cai, 2007; De Groef et al., 2013; Galton, 2005; Lamers

* Corresponding author.
E-mail addresses: y.watanabe@latrobe.edu.au (Y. Watanabe), s.grommen@latrobe.edu.au (S.V.H. Grommen), b.degroef@latrobe.edu.au (B. De Groef).

http://dx.doi.org/10.1016/j.ygcen.2016.02.012
0016-6480/

et al., 1986; Liggins, 1994; Wada, 2008). Thyroid hormones and corticosteroids act as developmental hormones, responsible for the differentiation and maturation of several organs in preparation of the individual for the new environment it is about to encounter. These processes are perhaps the most spectacular in anurans, but also occur in life stage transitions of other vertebrate groups. For example, thyroid hormones and corticosteroids regulate lung surfactant maturation in late embryos of various reptile species, such as green sea turtle (*Chelonia mydas*), bearded dragon (*Pogona vitticeps*), and saltwater crocodile (*Crocodylus porosus*) (Sullivan et al., 2001, 2002a,b). The development of the lung surfactant system is an important aspect of lung maturation, preparing the animal for a life outside the egg with pulmonary breathing. In addition to their developmental roles, corticosteroids and thyroid hormones are also important metabolic hormones that coordinate mobilization of energy stores during life stage transitions, for instance, by changing lipid metabolism from predominant lipogenesis to lipolysis during lamprey and anuran metamorphosis and during salmonid smoltification (Sheridan and Kao, 1998).

Corticosteroids and thyroid hormones often act synergistically during life stage transitions, in which these hormones modulate bioactivity of or tissue sensitivity to the other hormone (Bagamasbad and Denver, 2011; Denver et al., 2002; Denver, 2009; Kikuyama et al., 1993). Apart from this 'peripheral' crosstalk, both hormonal systems also cross over at the 'central' level: in various nonmammalian vertebrate species, but most likely not in mammals, corticotropin-releasing hormone (CRH) not only regulates the hypothalamo-pituitary-adrenal/interrenal (HPA/I) axis by stimulating adrenocorticotropic hormone (ACTH) release from the pituitary gland, but also controls the hypothalamo-pituitary-thyroid (HPT) axis by inducing the secretion of thyroid-stimulating hormone (TSH) (De Groef et al., 2006b). This raises the possibility that CRH plays a key role in the endocrine regulation of life stage transitions.

Here we will first review briefly what is known about the mechanistic basis of the synergistic interactions between corticosteroids and thyroid hormones during life stage transitions, *i.e.* the peripheral integration of the HPA/I and the HPT axes. We will then examine the available evidence supporting that CRH, as a central neuroendocrine controller of both the HPA/I and HPT axes, is the mediator of life stage transitions in various vertebrates. We will conclude this review with data that suggest that CRH has lost its thyrotropic activity in mammals.

2. Synergies of thyroid hormones and corticosteroids during life stage transitions

The importance of synergies between thyroid hormones and corticosteroids in vertebrate life stage transitions has been recognized for some time. Corticosteroids are long known to induce metamorphic changes when administered together with thyroid hormones *in vivo* and *in vitro* (Denver et al., 2002; Denver, 2009; Kikuyama et al., 1993). Synergies between thyroid hormones and corticosteroids were observed, for example, in the shrinkage of cultured tail segments of the common Japanese toad (*Bufo japonicus*) (Kikuyama et al., 1983) and in the artificial induction of morphological metamorphic changes in the pedomorphic axolotl (*Ambystoma mexicanum*) (Kühn et al., 2004). While ineffective in the absence of thyroid hormone, corticosteroid treatment also enhanced the effects of thyroid hormone on *in vitro* larval dorsal fin ray resorption of a flatfish, the Japanese flounder (*Paralichthys olivaceus*) (de Jesus et al., 1990, 1991). The synergistic effect of corticosteroids on thyroid hormone-regulated processes is based on several molecular mechanisms, as discussed below.

2.1. Effect of corticosteroids on thyroid hormone activation and inactivation

In most vertebrate species, the thyroid glands mainly produce thyroxine (T_4), which is generally considered to be a largely inactive prohormone that is transformed to the active hormone 3,3′, 5-triiodothyronine (T_3) in peripheral organs by outer-ring deiodination. Inner-ring deiodination of T_3 or T_4 produces inactive metabolites. Inner- and outer-ring deiodination reactions are catalyzed by iodothyronine deiodinases. Through effects on deiodinase activity and expression, corticosteroids can modify the sensitivity of tissues to thyroid hormone action (predominant local activation vs. predominant local inactivation), as well as alter the predominant thyroid hormone in the circulation (low vs. high plasma T_3), the latter mainly by modifying hepatic deiodinase activity.

Corticosteroids stimulate outer-ring deiodination, typically in a tissue- and developmental stage-specific manner, in a variety of species, including fish (*Solea senegalensis*: Arjona et al., 2011; *Fundulus heteroclitus*: Orozco et al., 1998; *Oreochromis niloticus*: Walpita et al., 2007), amphibians (*Lithobates catesbeianus*: Galton, 1990; axolotl: Darras et al., 2002; Kühn et al., 2005), embryonic saltwater crocodile (Shepherdley et al., 2002), embryonic chicken (Darras et al., 1996; Van der Geyten et al., 2001), and fetal sheep (Forhead et al., 2006; Wu et al., 1978). At least part of this effect is due to an effect of corticosteroids on deiodinase gene expression. Corticosteroids upregulate the transcription of the *dio2*/*DIO2* gene that encodes type 2 iodothyronine deiodinase (D2), an enzyme capable of converting T_4 to T_3, in the brain of embryonic chickens (Van der Geyten et al., 2001) and in *Xenopus laevis* tadpole tails (Bonett et al., 2010).

In addition, corticosteroids affect the activity and/or expression of type 3 deiodinase (D3), an enzyme that catalyzes inactivation of T_3 by inner-ring deiodination. In chicken embryos, administration of corticosteroids acutely decreased hepatic D3 activity, which was accompanied by an increase in plasma T_3 levels (Darras et al., 1996; Van der Geyten et al., 1999). This corticosteroid-mediated decrease in D3 is the result of a direct downregulation of hepatic *DIO3* gene transcription, but the molecular mechanism of this transrepression is unknown (Van der Geyten et al., 1999, 2001).

The D3-downregulating effect of corticosteroids may have a major role in the increase in circulating T_3 seen during many life stage transitions. In the embryonic chicken, hepatic D3 activity drops by ~98% towards hatching, when circulating T_3 levels peak (Darras et al., 1992). It is thought that a rise in circulating corticosteroids during the last week of embryonic development downregulates hepatic D3 activity, resulting in decreased T_3 inactivation and thus increased circulating T_3 levels which induce hatching. A similar series of events may occur during metamorphosis in flatfish (Isorna et al., 2009) and amphibians (Galton, 1990). Acute treatment with dexamethasone also decreased hepatic D3 activity in the axolotl, resulting in an increase in plasma T_3 levels. Chronic corticosteroid treatment furthermore elicited changes typical of metamorphosis, such as a reduction in gill length, tail height and body weight (Darras et al., 2002). In tails of *X. laevis* tadpoles treated *in vivo* with corticosterone, *up*regulation rather than downregulation of *dio3* mRNA was observed (Bonett et al., 2010). A recent microarray study by Kulkarni and Buchholz (2012), however, only found upregulated *dio3* expression in the tails of T_3-treated *Xenopus tropicalis* tadpoles, but not in tails of animals treated with a combination of T_3 and corticosterone.

2.2. Effect of corticosteroids on target tissue sensitivity for thyroid hormones

A second mechanism of thyroid hormone-corticosteroid synergy occurs at the level of thyroid hormone receptor (TR)