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Evolution of ligands, receptors and metabolizing enzymes of thyroid signaling

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ABSTRACT

Thyroid hormones (THs) play important roles in vertebrates such as the control of the metabolism, development and seasonality. Given the pleiotropic effects of thyroid disorders (developmental delay, mood disorder, tachycardia, *etc*), THs signaling is highly investigated, specially using mammalian models. In addition, the critical role of TH in controlling frog metamorphosis has led to the use of *Xenopus* as another prominent model to study THs action. Nevertheless, animals regarded as non-model species can also improve our understanding of THs signaling. For instance, studies in amphioxus highlighted the role of Triac as a *bona fide* thyroid hormone receptor (TR) ligand. In this review, we discuss our current understanding of the THs signaling in the different taxa forming the metazoans (multicellular animals) group. We mainly focus on three actors of the THs signaling: the ligand, the receptor and the deiodinases, enzymes playing a critical role in THs metabolism. By doing so, we also pinpoint many key questions that remain unanswered. How can THs accelerate metamorphosis in tunicates and echinoderms while their TRs have not been yet demonstrated as functional THs receptors in these species? Do THs have a biological effect in insects and cnidarians even though they do not have any TR? What is the basic function of THs in invertebrate protostomia? These questions can appear disconnected from pharmacological issues and human applications, but the investigation of THs signaling at the metazoans scale can greatly improve our understanding of this major endocrinological pathway.

1. Introduction

Thyroid hormones (THs) are involved in many biological processes in vertebrates (Holzer and Laudet, 2015), such as energy metabolism (reviewed in Mullur et al., 2014), thermoregulation (Lebon et al., 2001) but also development (Delange, 2001; Flamant et al., 2002; Göthe et al., 1999; Morte et al., 2002). In addition, THs are a critical signal triggering metamorphosis in amphibians as well as in many fishes, and are therefore important hormones that control the life cycle in vertebrates (Laudet, 2011). In humans, defects in THs signaling, either hyperthyroidism (too high THs concentration) or hypothyroidism (too low THs concentration), can lead to severe pathological conditions with a wide variety of symptoms such as tiredness, weight change, mood disorder, developmental delay, tachycardia. In addition, complete lack of THs is lethal. Thyroid cancers are the most common endocrine cancers with increasing incidence (Pacini et al., 2012). The primary treatment for such cancers is the complete or partial removal of the thyroid, leading to a massive disruption of the gland physiology (Pacini et al., 2012). Therefore, TH synthesis, its degradation and its signaling activity are the subject of many investigations.

Two molecules are collectively referred as THs: the native hormone thyroxine (3,3′,5,5′-T4 or T4), which represents 80% of the hormone synthesized by the thyroid (Sapin and Schlienger, 2003), and the active hormone triiodothyronine (3,3′,5-T3 or T3) that has a 10-fold higher affinity for the receptor than T4 (Chopra, 1976). T4 is used as a precursor by three specific enzymes, the deiodinases that synthesize both active and inactive TH derivatives by catalyzing the removal of iodine atom from T4. More specifically, two reactions are distinguished. The outer ring deiodination, catalyzed by the deiodinase type II (Dio2, Kuiper et al., 2005), transforms T4 in target

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tissues into T3 (Fig. 1). Dio2 is therefore considered as an activating deiodinase. It also turns T3 into 3,5-T2, a TH derivative long considered as inactive but for which accumulative evidences suggest a biological role (Lietzow et al., 2016; Mendoza et al., 2013). The inner ring deiodination is catalyzed by the deiodinase type III (Dio3) which is considered as an inactivating deiodinase as it turns T4 into reverse T3 (3-3′-5′-T3 or rT3) and T3 into 3-3′-T2 (Fig. 1), compounds that have no biological activity (Chopra et al., 1978; Moreno et al., 2003). This process is also referred as an inner ring deiodination. The deiodinase type I (Dio1) has both outer ring and inner ring deiodination activity but with a lower activity than Dio2 and Dio3. Although it is required to regulate the normal level of TH, its biological role is less clear (Maia et al., 2011).

THs act by binding to specific nuclear receptors: the thyroid hormone receptors (TRs), which belong to the nuclear receptor superfamily. TRs are ligand-dependent transcription factors that bind to DNA. TRs do not bind DNA alone but form a heterodimer with RXR, another nuclear receptor, and it is TR/RXR that forms the real functional unit of gene transcription control (Kojetin et al., 2015). In the classical view, TRs repress their target genes in absence of the ligand and activate them in presence of the ligand (reviewed in Gronemeyer et al., 2004). Some genes undergo a negative regulation by THs and are actively repressed by liganded TRs (Hollenberg et al., 1995; Matsunaga et al., 2015). Additionally, ligand binding influences the receptor binding on DNA (Ramadoss et al., 2014). This suggests that the biological reality of TR transcription regulation is more complex than the classical model (Flamant, 2016). There are two TRs in vertebrates, *TRα* and *TR*β that emerged from the whole genome duplication events at the basis of this group (Kuraku et al., 2008; Marchand et al., 2001; Smith et al., 2013). Teleost fishes underwent an additional specific whole genome duplication which results in two *TRα* genes, TRα-A and *TRα-B* (Escriva et al., 2004; Marchand et al., 2001).

However, TH signaling is not a vertebrate innovation (Paris et al., 2008a) and it is established that TH-signaling was functional at the base of chordates (Paris et al., 2008a) and even possibly at the base of the bilaterians (Bertrand et al., 2004; Wu et al., 2007). Moreover, the investigation in the invertebrate chordate amphioxus (*Branchiostoma* sp) suggests that the 3,5,3'-triiodo-thyroacetic acid (Triac), a deaminated derivative of T3 (Fig. 1), was a *bona fide* TRs ligand in the chordate common ancestor (Paris et al., 2008b). Thus, it is useful to describe what the studies of non-classical models bring to our understanding of TH signaling. In this review we will explore our current understanding of TH signaling in several metazoan groups starting from vertebrates toward more distant groups.

2. Even in vertebrates, the classical ligand can hide an astonishing diversity of active compounds

As introduced above, THs are involved in many biological processes. T3 is well acknowledged and recognized as the canonical ligand of TR in vertebrates. T4 is generally considered only as a precursor of T3 but several evidence, and in particular the recent detailed analysis of mouse strains in which the deiodinase genes have been inactivated, led to the suggestion that it may have a biological function in itself via TRs (Galton, 2017). However we will not discuss much T4 and T3 here as the latest discoveries on their biological role are covered in other chapter of this issue. We will discuss here whether other molecules could be considered as ligand and the role of the deiodinases in the modulation of TH signaling.

As previously mentioned, there are two paralogs of vertebrate TRs, *TRα* and *TR*β, which originate from the two rounds of whole genome duplication that happened at the base of all vertebrates (Kuraku et al., 2008). This duplication allows the divergence of the two copies in terms of amino acid sequence and regulatory sequence. In the mouse, *TRα* and *TRβ* regulate different subsets of

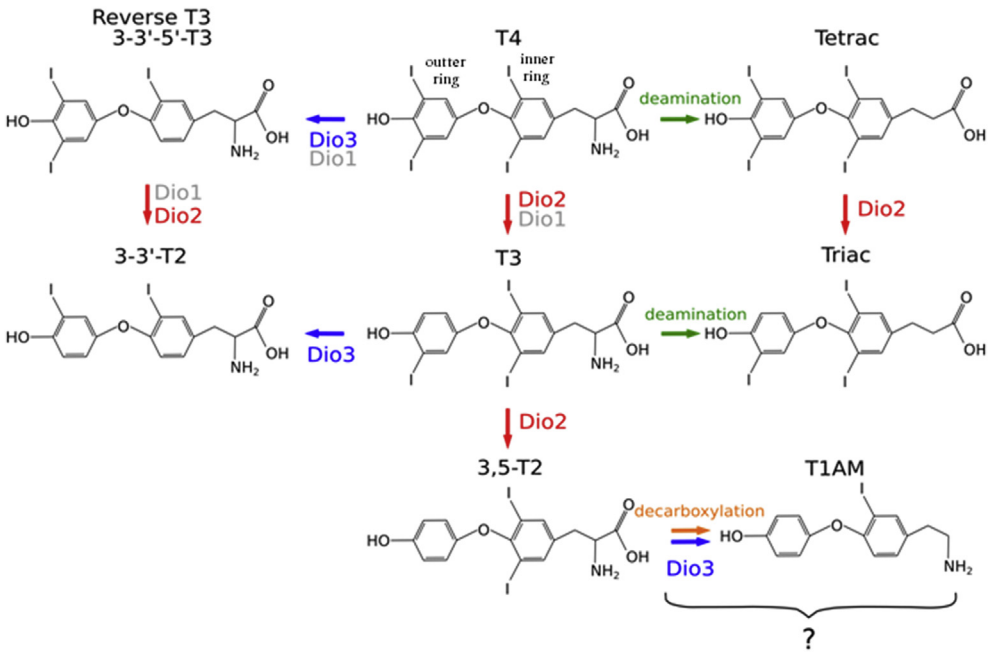

Fig. 1. The classical TH derivatives. Inner and outer rings are indicated above T4. Red arrows indicate outer ring deiodination performed by Dio2. Blue arrows indicate inner ring deiodination performed by Dio3. Grey arrows indicate deiodination performed by Dio1. Green arrows indicate deaminations. The orange arrow indicates a decarboxylation. The interrogation mark under the T1AM indicates that although possible from TH, the synthesis of this compound remains unknown. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

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