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Review

Intracellular thyroid hormone metabolism as a local regulator of nuclear thyroid hormone receptor-mediated impact on vertebrate development ☆

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ABSTRACT

Background: Thyroid hormones (THs) play an essential role in vertebrate development, acting predominantly via nuclear TH receptors (TRs) which are ligand-dependent transcription factors. Binding of the ligand (predominantly T_3) induces a switch from gene activation to gene repression or vice versa. Iodothyronine deiodinases (Ds) and TH transporters are important regulators of intracellular T_3 availability and therefore contribute to the control of TR-dependent development.

Focus: The present review discusses the possible roles of Ds and TH transporters in regulating embryonic and larval (pre-juvenile) TR-dependent development in vertebrates. It focuses mainly on well-known model species for direct and indirect vertebrate development, including zebrafish, *Xenopus*, chicken and mouse. Data are provided on stage- and tissue/cell-specific changes in expression of Ds and TH transporters. This information is combined with functional data obtained from gain-and-loss of function studies.

Conclusion: Knockout/knockdown of each type of D has provided strong evidence for their implication in the control of important developmental processes and several D expression patterns and functions have been conserved throughout vertebrate evolution. Knockout/knockdown of the inactivating D3 enzyme indicates that a premature switch from unliganded to liganded TR action is often more detrimental than a delayed one. The majority of ontogenetic studies on TH transporter distribution and function have focused on brain development, showing variable impact of knockout/knockdown depending on the species. Future research in different models using conditional silencing will hopefully further improve our understanding on how TH transporters, Ds and TRs cooperate to regulate TR-mediated impact on vertebrate development. This article is part of a Special Issue entitled: Nuclear receptors in animal development.

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1. Introduction

Thyroid hormones (THs) play an essential role in vertebrate development. As a result, TH deficiency not only delays normal development, but it also results in irreversible lifelong defects, especially in the nervous system. In vertebrates with a clear metamorphosis, such as amphibians and many fish, TH deficiency will even stop progress from a larva into a juvenile and eventually result in death. THs mainly act by binding to nuclear TH receptors (TRs) that control transcription of TH-responsive genes. Many of them are important regulators of developmental processes, including cell division, differentiation, migration and apoptosis. Vertebrates have two types of nuclear TRs, TRα and TRβ, encoded by *thra* and *thrb* respectively. Each gene can give rise to different receptor isoforms via alternative splicing and each isoform has specific functions [1,2]. However, almost all hormone binding TRs have a higher affinity for 3,5,3′-triiodothyronine (T_3) as compared to 3,5,3′,5′-tetraiodothyronine or thyroxine (T_4), making T_3 the predominant hormone active at the level of the nuclear TRs in most vertebrates. Teleosts were recently shown to have two variants of TRβ1. While the short variant predominantly binds T_3, the long variant binds with high affinity to 3,5-diiodothyronine (3,5-T_2) and both hormones are physiologically relevant in regulating gene expression [3,4].

2. Need for local regulation of TH availability

The only cells capable of producing THs are the follicular cells of the thyroid gland. This gland mainly releases T_4 while T_3 is released in minor amounts. During the early stages of development, embryos are not yet able to synthesize their own THs. They therefore rely on maternal THs that are deposited in the yolk or supplied via the placenta in the

Abbreviations: D1, D2, D3, iodothyronine deiodinase types 1, 2, and 3; KD, knockdown; KO, knockout; LAT1, LAT2, L-type amino acid transporters 1 and 2; MCT8, MCT10, monocarboxylate transporters 8 and 10; OATP1C1, organic anion transporting polypeptide 10; TH, thyroid hormone; TRα, TRβ, thyroid hormone receptors α and β

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case of mammals. As development progresses and the embryonic thyroid gland starts functioning, the relative contribution of maternal THs gradually declines. Maternal and embryonic THs are transported via the circulation throughout the body to reach the different tissues and the amount of hormone in circulation changes according to a species-specific ontogenetic pattern. However, embryonic or larval tissues do not all develop in the same way nor at the same rate. Therefore different tissues/cell types need several mechanisms to modulate the impact of circulating THs according to their specific needs at a given time.

One common mechanism to regulate local hormone action is by changing the expression of hormone receptors. The expression of different TRs indeed changes throughout development in a tissue-specific way [5–7]. However, TRs not only function when bound to their ligand since unliganded TRs also bind to TH-response elements (TREs) in the promotor region of TH-responsive genes. In case of a positive TRE, binding of the ligand can acutely reverse TR impact from repression to stimulation of gene transcription while in case of a negative TRE the opposite may occur [2,8,9]. Changes in intracellular ligand availability are therefore an essential level to regulate TR-mediated action. Intracellular iodothyronine deiodinases are important in this process since these enzymes can locally produce or degrade T_3 as well as 3,5-T_2 [4]. TH transporters located in the plasma membrane are important as well, since they control influx of THs into the cell as well as TH efflux (Fig. 1). The present review focuses on the role of changes in iodothyronine deiodinases and TH transporters in vertebrate development, while other reviews in this special issue on Nuclear Receptors in Animal Development focus more specifically on the changes at the level of the TRs.

3. Iodothyronine deiodinases and vertebrate development

Vertebrates possess three types of iodothyronine deiodinases (D1, D2, D3) encoded by *dio1*, *dio2* and *dio3* respectively [10–12]. D1 is a multifunctional enzyme that can cleave iodine from the outer as well as the inner ring of an iodothyronine. It is a high Km enzyme that can convert T_4 into T_3 and as such contributes to circulating T_3 levels. Its preferred substrate is however reverse T_3 (rT_3) and studies in D1-deficient mice suggest that D1 functions primarily as a scavenging enzyme, important in iodine recycling from inactive and lesser iodothyronines [13,14]. D2 only catalyses outer ring deiodination (ORD); it is a low Km enzyme with T_4 as major substrate. It is important for local T_3 production in several tissues but also contributes to circulating T_3, especially in fish and amphibians. It is also a likely candidate to convert T_3 into 3,5-T_2, which binds to the long variant of TRβ1 in teleosts [3]. D3 is also a low Km enzyme that catalyses only inner ring deiodination (IRD) and has T_3 as preferred substrate. Its main function is the conversion of T_3 as well as T_4 into iodothyronines that do not bind to nuclear TRs. In general, a given cell type expresses either one or two types of Ds but the number and type may change several times during ontogeny.

Development in vertebrates can be either direct or indirect. In mammals, birds and reptiles the process of birth (following internal development) or hatching (following external development) marks the direct transition from the embryo to the juvenile, immature adult form. Amphibians and fish have an indirect development where hatching is followed by a distinct larval phase separating the embryo and the juvenile. This review focuses on some well-studied species with indirect/direct development to illustrate the impact of Ds on each of the pre-juvenile stages and on the sequential transition from one stage to the other. Whenever possible, we try to combine information on D ontogenetic expression patterns with information gained from gain-and-loss of function studies.

3.1. Indirect development in fish and amphibians

3.1.1. Zebrafish embryos

Embryonic D expression has been studied in detail in zebrafish (*Danio rerio*), one of the major vertebrate models for developmental biology. Zebrafish embryonic development takes about 3 days and their thyroid gland starts hormone secretion around hatching [15]. Due to a whole genome duplication in the early evolution of ray-finned fishes, zebrafish and several other teleost fish have two *dio3* paralogues [16,17], similar to the presence of two *thra* paralogues [18].

Maternal mRNA for all three types of Ds is present in the egg and by the end of the maternal–zygotic transition around 8 h post fertilisation (8 hpf) embryonic transcripts can be detected and quantified. While whole body *dio1* and *dio3* mRNA levels increase during the first day of embryogenesis, *dio2* mRNA levels only rise substantially on the third day, around hatching concomitant with the start of embryonic TH secretion ([17,19]; and own unpublished results) (Fig. 2). In situ hybridization (ISH) results on the tissue-specific expression pattern in zebrafish embryos have been reviewed recently [20]. At 12 hpf the *dio1* and *dio2* signals are colocalized in the head region while the *dio3* signal is found in the kidney. From 24 hpf onwards *dio2* is also expressed in the retina and the adenohypophysis. At 48 hpf *dio2* also appears in the spinal cord and *dio1* can be detected in the liver [21–23].

Thanks to the relatively easy method of antisense morpholino injection [24] loss-of-function studies in zebrafish embryos have been possible for all three Ds. Knockdown (KD) of D2 clearly delays development

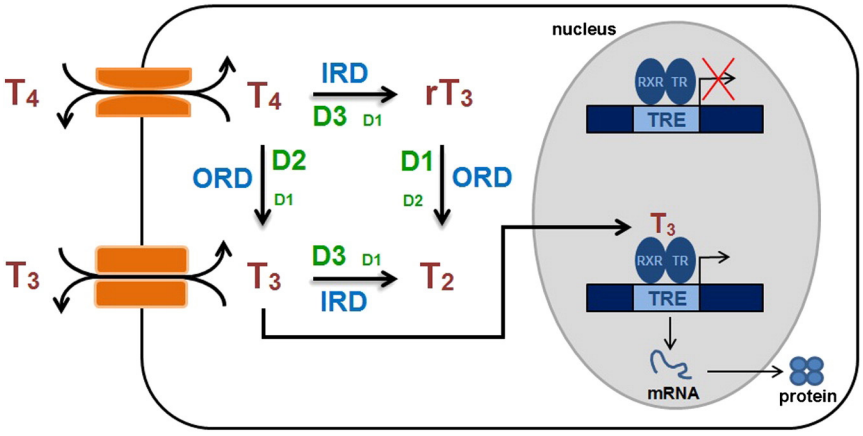

Fig. 1. Intracellular T_3 availability and action. Specific TH transporters facilitate the influx as well as the efflux of T_4 and T_3 (and some other iodothyronines). Within the cell, different deiodinases (Ds) activate or inactivate THs, thereby regulating T_3 availability. T_3 translocates to the nucleus where it binds to TH receptors (TRs). TRs form heterodimers (predominantly with the retinoic X receptor, RXR) and bind to TH response elements (TREs) in the promoter region of TH-responsive genes. The figure represents the situation for positively regulated genes where unliganded TRs repress gene transcription, while binding of T_3 induces a switch from repression to activation of gene transcription. The opposite occurs for negatively regulated genes.

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