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Autoinduction of nuclear hormone receptors during metamorphosis and its significance

Jamshed R. Tata *

National Institute for Medical Research, The Ridgeway, Mill Hill, London NW7 1AA, UK

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Abstract

Metamorphosis is a most dramatic example of hormonally regulated genetic reprogramming during postembryonic development. The initiation and sustenance of the process are under the control of ecdysteroids in invertebrates and thyroid hormone, 3,3′,5-triiodothyronine, in oviparous vertebrates. Their actions are inhibited or potentiated by other endogenous or exogenous hormones — juvenile hormone in invertebrates and prolactin and glucocorticoids in vertebrates. The nuclear receptors for ecdysteroids and thyroid hormone are the most closely related members of the steroid/retinoid/thyroid hormone receptor supergene family. In many pre-metamorphic amphibia and insects, the onset of natural metamorphosis and the administration of the exogenous hormones to the early larvae are characterized by a substantial and rapid autoinduction of the respective nuclear receptors. This review will largely deal with the phenomenon of receptor autoinduction during amphibian metamorphosis, although many of its features resemble those in insect metamorphosis.

In the frog *Xenopus*, thyroid hormone receptor autoinduction has been shown to be brought about by the direct interaction between the receptor protein and the thyroid-responsive elements in the promoter of its own gene. Three lines of evidence point towards the involvement of receptor autoinduction in the process of initiation of amphibian metamorphosis: (1) a close association between the extent of inhibition or potentiation by prolactin and glucocorticoid, respectively, and metamorphic response in whole tadpoles and in organ and cell cultures; (2) thyroid hormone fails to upregulate the expression of its own receptor in obligatorily neotenic amphibia but does so in facultatively neotenic amphibia; and (3) dominant-negative receptors known to block hormonal response prevent the autoinduction of wild-type *Xenopus* receptors in vivo and in cell lines.

Autoinduction is not restricted to insect and amphibian metamorphic hormones but is also a characteristic of other nuclear receptors (e.g., retinoid, sex steroids, vitamin D_3 receptors) where the ligand is involved in a postembryonic developmental function. A wider significance of such receptor autoregulation is that the process may also be important for mammalian postembryonic development.

Keywords: Amphibian metamorphosis; Thyroid hormone; Prolactin; Thyroid hormone receptors; Receptor autoinduction

1. Introduction

Thyroid hormone (TH) is synthesized and secreted in virtually every cold- and warm-blooded vertebrate examined (Gorbman and Bern, 1962). During evolution it has been put to different uses in different organisms as a hormonal signalling molecule, thus generating a remarkable multiplicity of physiological actions. With the discovery that thyroid hormone receptor (TR) is a member of the nuclear steroid/thyroid hormone super-gene family (Mangelsdorf and Evans, 1995; Chatterjee et al., 1997; Tata, 1998), and that the dynamics of transcriptional stimulation and receptor occupancy in the nucleus are very intimately linked in vivo (Oppenheimer and Samuels, 1983), TR now occupies a central position in our thinking about the mechanism of action of thyroid hormone. This is particularly true for elucidating its growth and developmental actions. The rapid advances in gene technology in the last two decades have revealed that TRs are highly conserved. It is generally accepted that the primary intracellular event is the interaction between TR and its ligand in the cell nucleus, and that the diversity of actions of TH is generated by species- and tissue-specific factors and mechanisms.

* Tel.: +44-181-959-3666; fax: +44-181-913-8583.
E-mail address: jtata@nimr.mrc.ac.uk (J.R. Tata).

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2. Amphibian metamorphosis

Following the discovery by Gudernatsch (1912) that frog larvae fed on extracts of mammalian thyroid glands underwent precocious metamorphosis spontaneously, detailed analysis of the functional role of the developing larval thyroid gland, and the availability of pure L-thyroxine, confirmed that the process of metamorphosis was obligatorily dependent on thyroid hormone.

This obligatory requirement of thyroid hormone for amphibian metamorphosis offers an ideal model to explore its developmental actions in vertebrates, in the same way as for ecdysteroids in invertebrates. This similarity can be discerned from Fig. 1, which depicts how environmental cues and neuroendocrine cascades initiate metamorphosis in amphibia (Gilbert et al., 1996; Tata, 1997). Thyroid hormone provokes diverse and multiple morphological, physiological and biochemical responses in virtually every tissue of the amphibian tadpole, some of which are listed in Table 1 for different tissues of the pre-metamorphic tadpole. These range from de novo morphogenesis, repatterning, functional reprogramming, and partial and total regression. Before extending this article to its receptors, it is useful at this point to briefly consider the special characteristics of the role of TH in amphibian metamorphosis.

The thyroidectomized anuran larva will continue to grow without undergoing metamorphosis until administration of L-thyroxine (T_4) or 3,3′,5-triiodo-L-thyronine (T_3) at any stage thereafter causes resumption of the arrested differentiation and leads to metamorphosis. This not only establishes the obligatory requirement of TH for metamorphosis but also indicates that the genetic programme for this postembryonic development is stable and not determined temporally. The competence for metamorphosis is established well before the tadpole's thyroid gland has developed functionally (Tata, 1968), which means that TR must be expressed constitutively early in development. Transplantation and organ culture studies with early tadpole tissues established that the hormone does not determine the developmental programme but only initiates it, and that it can induce diametrically opposite developmental changes in different tissues (Tata et al., 1991; Ishizuya-Oka and Shimozawa, 1991).

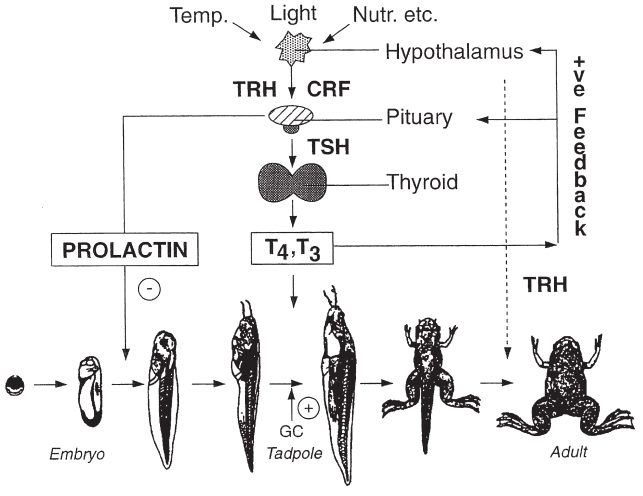

Fig. 1. Schematic representation of the hormonal regulation of amphibian metamorphosis. In response to environmental cues, the dormant thyroid gland of the tadpole is activated to produce the thyroid hormones T_4 and T_3 by the hypothalamic and pituitary hormones TRF, CRF and TSH. Thyroid hormone (TH) is obligatorily required to initiate and maintain the metamorphosis, its action being potentiated by glucocorticoid hormone and retarded by prolactin. Nutr., nutritional factors; TRH, thyrotrophin-releasing hormone; CRF, cortcotrophin-releasing factor; TSH, thyoid-stimulating hormone; T_4, L-thyroxine; T_3, triiodo-L-thyronine; GC, glucocorticoid hormone.

Although the culture studies confirmed that TH acts directly on its target tissues, it is also known that other hormones, factors released by neighbouring tissues or environmentally transmitted signals can modify the response of a given tissue to TH. Among important endocrine factors are glucocorticoid hormone (GC), corticotrophin-releasing hormone (CRF) and prolactin (PRL). As seen in Fig. 1, exogenous GC and CRF are known to potentiate, while PRL blocks, both natural and TH-induced metamorphosis in whole tadpoles and organ cultures (Kikuyama et al., 1993; Tata, 1997). The modulation of TH action by glucocorticoids and PRL has provided a useful tool in analysing the action of TH, especially in organ cultures of tadpole tissues.

Some of the responses of the amphibian larval tissues to TH, seen in Table 1, are the manifestation of a new genetic programme activated by the hormone, whereas others represent the acceleration or slowing down of the expression of a programme that had already been initiated before the action of the hormone (Tata, 1997). It is well known that stimulation of transcription is one of the earliest biochemical responses of *Xenopus* tadpole tissues to exogenous T_3, and that blocking the stimulation of transcription will prevent most of the downstream biochemical and physiological responses to TH (Tata 1966, 1998). What is of particular interest also are the direct-response genes, namely those whose transcription is initiated by TH in the presence of inhibitors of protein synthesis. Brown, Shi and colleagues have been able to classify genes in *Xenopus* tadpoles which are up- or downregulated by T_3 and those that are direct-response genes (Shi, 1996). Most direct-response genes are upregulated during metamorphosis, even in tissues programmed for total tissue regression.

A major characteristic of metamorphosis is the substantial apoptosis, restructuring and further differentiation of tissues such as the tail, brain, limb buds, intestine and pancreas (Tata, 1994). The use of inhibitors of protein synthesis has demonstrated that cell death is dependent on the de novo synthesis of new proteins, this requirement for new protein synthesis for the onset of

Table 1
Diversity of morphological and biochemical responses to thyroid hormone during amphibian metamorphosis

Tissue	Response	
	Morphological	Biochemical
Brain	Restructuring; axon guidance and growth; cell turnover	Cell division; apoptosis; protein synthesis
Liver	Functional differentiation; restructuring	Induction of albumin and urea cycle enzymes; larval–adult haemoglobin switch
Eye	Repositioning; new retinal neurones; altered lens	Visual pigment switch; induction of β-crystallin
Skin	Restructuring; keratinisation; granular gland formation	Induction of collagen, 63 kDa keratin, magainin
Limb bud, lung	De novo morphogenesis of bone, skin, muscle, nerve, etc.	Cell proliferation; gene expression
Tail, gills	Total tissue regression and removal	Programmed cell death; induction of lytic enzymes
Intestine, pancreas	Major remodelling of tissues	New structural and functional constituents
Immune system	Redistribution of immune cell populations	Aquisition of new immunocompetence
Muscle	Growth, differentiation, apoptosis	Induction of myosin heavy chain

apoptosis being a common feature of programmed cell death during development.

3. Thyroid hormone receptors

The interaction between thyroid hormone and its receptors in the cell nucleus is the crucial step that initiates the molecular and biochemical chain of events leading to the physiological response of the target cell to the hormone.

TRs are members of an evolutionarily highly conserved supergene family of steroid/thyroid hormone/retinoid nuclear receptors that function as ligand-inducible transcription factors (Mangelsdorf and Evans, 1995; Chatterjee et al., 1997; Laudet et al., 1992; Baniahmad et al., 1997). In all vertebrates they are encoded by two genes, termed TRα and TRβ, from which are generated multiple isoforms according to the tissue and species. The modular structure of nuclear receptors comprising the *N*-terminus, DNA-binding and ligand-binding domains is now well known. TRs belong to the subgroup that includes nuclear receptors for retinoic and 9-*cis*-retinoic acids (RARs and RXRs, respectively), vitamin D_3 (VDR) and peroxisome proliferators (PPAR). Unliganded TRs are constitutively located in the nucleus as components of chromatin; by combining with TRs, T_3 activates the transcription of its target genes by interacting with thyroid-response elements (TREs) in their promoters, the most common motif being AGGTCAnnnnAGGTCA and known as direct repeat plus 4 (DR+4).

The mechanism by which TR regulates transcription is not fully understood, but three important features of the receptor are relevant (Chatterjee et al., 1997). First, unlike other nuclear receptors, unliganded TR acts as a strong repressor, the repression being relieved by the ligand. Second, although TR monomer and homodimer can interact with TRE, the physiologically active form is the heterodimer formed with RXR, a property also shared by other members of its subgroup of nuclear receptors. Third, two groups of proteins that have recently been identified as co-repressors (CoR) or co-activators (CoAc) are thought to be essential for the transactivation function of the receptor. The role of hormone binding to the ligand-binding domain of TR would be to cause the dissociation of CoR from its inactive complex with the receptor while at the same time facilitating the recruitment of CoAc to form a transactivational complex. Also recently, much interest has been generated by the finding that co-repressors and co-activators have histone acetylase or deacetylase activities (Pazin and Kadonaga, 1997; Wong et al., 1998). It will not be surprising that more components participating in such complexes and structurally organized as chromatin are discovered in the near future.

4. Autoregulation of TRs during metamorphosis

In *Xenopus* tadpoles normal metamorphosis does not begin until the larval thyroid gland becomes functional, which can be about six weeks after fertilization. The onset and rapid acceleration of metamorphosis correlates well with the build-up of circulating T_3 (Tata, 1997). The fact that competence to respond to exogenous TH is established as early as one week after fertilization (Tata, 1968) means that functional TR is present well before the secretion of the hormone. Hence it was not surprising that both TRα and β mRNA and protein can be detected in most tissues of the early pre-metamorphic larvae (Eliceiri and Brown, 1994; Fairclough and Tata, 1997), indicating the constitutive expression of TRs at low levels. There is also strong correlation between the accumulation of TR mRNA and protein and the rising levels of TH. Upon completion of metamorphosis the

concentrations of all three constituents decline very sharply. This correlation raised the question as to whether the hormone itself regulates the expression of its own receptor genes.

Biochemical, in situ hybridization and immunocytochemical analyses of TR mRNAs and proteins have clearly shown that exogenous TH can precociously upregulate TR gene expression in all tissues of the pre-metamorphic tadpole, irrespective of whether or not they undergo de novo morphogenesis, total regression or restructuring (Tata, 1997; Shi, 1996). The upregulation of TR genes, which can also be reproduced in *Xenopus* cell lines with similar kinetics to those seen in whole tadpoles, is among the most rapid responses to TH in amphibia, is more marked for the β than the α gene, and is the result of direct activation of their transcription (Tata et al., 1993; Kanamori and Brown, 1992; Machuca and Tata, 1992; Tata, 1996). The advantage of studying receptor autoinduction in tissue culture is not only greater precision in establishing its kinetics, but it also allows one to investigate the mechanism of the process by DNA transfection.

The possibility that TR can interact with its own gene promoter to produce the autoinduction was strengthened by the finding that the *Xenopus* TR promoter comprises two or more functional DR+4-type TRE sequences (Ranjan et al., 1994; Machuca et al., 1995). These studies also demonstrated that TR–RXR heterodimers, but not TR monomers or homodimers, specifically interacted with TREs in the promoter of the *Xenopus* TRβ gene, and that the heterodimer could regulate the transcription of TR. However, since RXRs are also heterodimeric partners of other nuclear receptors (Chambon, 1995; Mangelsdorf and Evans, 1995), it is not surprising that the expression of RXR does not closely parallel that of TR genes during the autoinduction process in *Xenopus* tissues (Iwamuro and Tata, 1995).

Further evidence that TRs could act directly on the promoters of their own genes has come from studies on dominant-negative (d-n) TRs in whole *Xenopus* tadpole tissues and cell lines (Ulisse et al., 1996). A large number of d-n TRβ1 mutant receptors in man, associated with the syndrome of generalized thyroid hormone resistance, have been shown to bind TREs, but not TH, and inhibit transactivation by wild-type TRs in a dominant-negative manner (Refetoff et al., 1993). It is therefore significant that human mutant TRβs and a synthetic mutant *Xenopus* TRβ were able to inhibit autoinduction of wild-type TRβ when transfected into XTC-2 cells, in a manner whereby the strength of the dominant-negative effect of the mutant TRs correlated well with the dose of T_3, heterodimerization with RXR and the binding of the heterodimers with various TREs (Ulisse et al., 1996). More interestingly, transfection of tadpole tail muscle in vivo showed that d-n mutant TRs prevented wild-type TRβ autoinduction in pre-metamorphic *Xenopus* tadpole tissues. These results now lead to the important question of how relevant is the autoinduction of TR to the process of metamorphosis itself.

5. Significance of autoinduction of TRs during amphibian metamorphosis

There is good indirect evidence from two separate observations of an intimate relationship between TR gene expression and the regulation of amphibian metamorphosis by thyroid hormone.

There is good correlation between the inhibition and potentiation of metamorphosis by PRL and GC, respectively, and the inhibition or enhancement of autoinduction of TR and RXR genes in several tadpole tissues during natural or T_3-induced metamorphosis (Baker and Tata, 1992; Tata, 1997). This correlation is particularly marked for the antagonism between TH and PRL, as can be discerned from Table 2.

PRL blocks the upregulation of both TRα and β mRNAs induced by T_3, but does not affect the constitutive expression of the receptor genes in whole pre-metamorphic tadpoles and in organ cultures. The conclusion that TR autoinduction is necessary for the activation of downstream TR target genes is further supported by the inhibition by PRL of the activation by T_3 of the downstream genes encoding albumin, 63 kDa keratin and stromelysin-3 genes. Interestingly, the synthetic glucocorticoid dexamethasone, which potentiates T_3-induced metamorphosis, elevates the levels of both TR and RXR mRNAs but PRL suppresses only that of TR when all three hormones are added to organ cultures of pre-metamorphic *Xenopus* tadpole tails. The mechanism of the anti-metamorphic action of PRL in amphibia remains unknown.

Another indirect indication that the autoinduction of TR genes is closely linked to amphibian metamorphosis comes from comparative studies of TR in neotenic amphibia, i.e., those that do not undergo metamorphosis

Table 2
Relative accumulation of TRα and β mRNAs in pre-metamorphic *Xenopus* tadpoles treated with T_3 and prolactin (PRL)[a]

Treatment	Relative units	
	TRα	TRβ
None	505	24
T_3	1290	368
T_3+PRL	799	10
PRL	405	43

[a] Batches of 20 stage 50 *Xenopus* tadpoles were treated with 2×10^{-9} M T_3 with or without 0.1 iu PRL/ml for 4 days before relative amounts of TR mRNAs were measured in total larval RNA by RNase protection assay.

Table 3
Association between TR autoinduction and response to thyroid hormones (T_3, T_4) of spontaneously metamorphosing and facultatively or obligatorily neotenic amphibia

Species	Metamorphosis	Endogenous T_3,T_4	TR genes	
			Expressed[a]	Autoinduced[b]
Xenopus	Spontaneous	Yes	Yes	Yes
Ambystoma	Facultatively neotenic	No	Yes	Yes
Necturus	Obligatorily neotenic	Yes	Yes	No

[a] Only TRα detectable in *Necturus*.
[b] By exogenous TH.

spontaneously (Tata et al., 1993; Yaoita and Brown, 1990; Safi et al., 1997). Facultatively neotenic amphibia such as the mexican axolotl or the tiger salamander (*Ambystoma*), which do not go through metamorphosis normally, will do so if exogenous TH is given, while obligatory neotenic amphibia such as *Necturus* and *Proteus* do not respond to TH. As can be seen in Table 3, low levels of TR mRNAs can be detected in *Ambystoma* tissues which can be upregulated by the administration of T_3, in parallel with a partial metamorphic response (loss of tail fin, growth of limbs, excretion of nitrogen as urea), as in *Xenopus*. In contrast, only TRα transcripts could be detected in tissues of *Necturus* in which T_3 failed to upregulate the expression of TRα or β mRNA.

6. Auto-upregulation of other nuclear receptors

The phenomenon of autoinduction is not restricted to thyroid hormone receptors but has been observed for other nuclear receptors of growth and developmental hormones and signals (Tata et al., 1993; Tata, 1996). Some examples of auto-upregulation of nuclear receptors are presented in Table 4. Of some relevance to TRs are the three isoforms of receptors for retinoic acid (RARs) which is well known to serve an important function in mammalian early embryogenesis and postembryonic development (Chambon, 1995). These three receptor genes are all induced by retinoic acid and, interestingly, they also contain retinoic-response elements in their promoters through which the liganded receptor regulates its own gene (Tata, 1998). Of greater relevance, however, to this conference on juvenile hormone (JH) is the autoinduction of ecdysteroid receptors (EcRs) in insects. Furthermore, among all the members of the steroid/thyroid hormone/retinoic acid nuclear receptor supergene family, TRs and EcRs are the most closely related members (Mangelsdorf and Evans, 1995). Thummel's and Riddiford's groups have established accurately the temporal coordination of EcR expression with that of other regulatory genes before, during and after different stages of natural metamorphosis and following pulses of exogenous ecdysone in *Drosophila* and *Manduca*, respectively (Thummel, 1996; Hiruma et al., 1999). It is therefore most significant that juvenile hormone has recently been shown to prevent the autoinduction of EcR-A and EcR-B1 mRNAs in larval epidermis of *Manduca* (Hiruma et al., 1999). It is not known whether the mechanism of this inhibitory effect of JH in invertebrates is comparable to that of prolactin in amphibia. What can, however, be concluded from the examples cited in Table 4 is that nuclear receptor autoinduction is a general phenomenon during postembryonic development.

Table 4
Autoinduction of nuclear receptors by some hormones while exerting their growth and developmental actions

Hormone and receptor	Species and tissue	Response
Thyroid hormone	All amphibian tissues	Metamorphosis
	Rodent astrocytes	Brain development
Estrogen	Avian and amphibian liver and oviduct	Vitellogenesis and egg maturation
Ecdysone	All insect cells	Metamorphosis
Retinoic acid	Rodent and avian brain, limbs, etc.	Morphogenesis
Androgen	Mammalian male sexual accessory tissues	Sexual maturation

7. Significance of autoinduction of nuclear receptors

There is now good evidence to suggest that receptor upregulation can be closely linked to the biological activity of its ligand. The model presented in Fig. 2, larg-

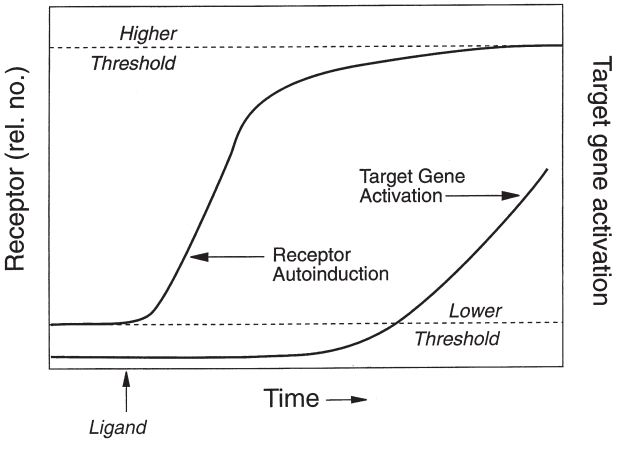

Fig. 2. A dual-threshold model to explain the physiological significance of autoinduction of nuclear receptors in hormonally regulated developmental processes (see text for explanation).

ely based on the autoinduction of TR during amphibian metamorphosis, is generally applicable to to all nuclear receptors in the context only of a developmental action of their respective ligands (Tata 1996, 1998). If upregulation of a given receptor is a neccessary first step leading to the sequential activation of its target genes whose products specify the final biological action, the model predicts a possible dual threshold of receptor numbers underlying the process of receptor autoinduction, on the one hand, and the activation of the target genes on the other. Thus, the genes encoding the relevant nuclear receptors would be constitutively expressed to produce very low levels of functional receptor in the target tissues from the very early stages of development. The unliganded receptor would be inactive or, as in the case of TR, may even act as a strong transcriptional repressor of genes with TREs in their promoters. Upon functional maturation of the appropriate endocrine gland and secretion of the hormone, or administration of exogenous hormone, the low levels of the liganded receptor would be sufficient to activate the genes encoding its own receptor but not for the receptor's target genes. For the latter, it is proposed that, as the concentration of the hormone reaches higher levels, concentrations of the liganded receptor, well above the lower threshold levels required to upregulate its own receptor, would now be able to activate different sets of genes in different tissues, each depending on distinct developmental programmes. An intriguing question relates to the factors involved in maintaining low levels of a given receptor prior to the onset of a developmental change and high levels during the change or inductive process. One such factor could be the involvement of other hormones or signalling molecules, as exemplified by prolactin and glucocorticoids in TH-regulated metamorphosis.

Hormonal cross-regulation of nuclear receptors is therefore an impotant additional consideration.

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