Amphibian metamorphosis as a model for studying the developmental actions of thyroid hormone

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SUMMARY - A salient feature of the thyroid hormones, L-thyroxine (T4) and triiodo-L-thyronine (T3), is the multiplicity of their physiological and biochemical actions in a wide variety of vertebrates. Important among these is their profound effects on postembryonic development. Analysis of their developmental action in mammals is vitiated by the exposure of the developing fetus to a number of maternal factors which do not allow one to specifically define the role of thyroid hormone (TH) or that of other hormones and factors that modulate its action.

Amphibian metamorphosis is obligatorily dependent on TH which can initiate all the diverse physiological manifestations of this postembryonic developmental process (morphogenesis, cell death, re-structuring, etc.) in free-living embryos and larvae of most anurans. It is therefore an ideal model for studying the mechanisms underlying the hormonal regulation of postembryonic development.

This article will first summarize the key features of metamorphosis and its control by TH and other hormones. Emphasis will be laid on the important role played by TH receptor (TR), in particular the phenomenon of TR gene aut induction, in initiating the developmental action of TH. For this reason, it will be argued that the findings on the control of amphibian metamorphosis enhance our understanding of the regulation of postembryonic development by TH in mammals and other vertebrate species.

INTRODUCTION

Well before the chemical identification of L-thyroxine (T4) and 3,3',5-triiodo-L-thyronine (T3) as thyroid hormones, the secretions of thyroid gland were known to regulate growth and development in a variety of vertebrates (18, 33, 36).

Observations on goitre, abnormal development and mental retardation in young children had indicated two centuries ago the close relationship between thyroid hormone in foetal and prenatal human development and, especially, neuronal maturation. Studies on the restoration of growth and maturation of the skeletal system in thyroidectomized and hypophysectomized neonatal rats established experimentally the growth and developmental action of T4 and its interaction with growth hormone. The demonstration that T4 is converted intracellularly to T3, the active form of thyroid hormone (TH), has
made it easier to follow the biochemical and molecular events that underlie the cellular actions of thyroid hormone (7, 26). As knowledge of the physiological and biochemical actions of thyroid hormone in different species and tissues progressed, a major characteristic of this hormone emerged, namely the multiplicity of its actions.

MULTIPlicity OF ACTIONS OF THYROID HORMONE

Thyroid hormones are synthesized and secreted in virtually every cold- and warm-blooded vertebrate examined (18). During evolution they have been put to different uses in different organisms as hormonal signalling molecules, thus generating a remarkable multiplicity of physiological actions. Table I lists the major physiological actions of TH in some vertebrates. These have been arbitrarily divided into actions that can be considered as regulating growth and development and those that control metabolic functions, although these are not mutually exclusive in some cases. For example, in postnatal mammals TH exerts a strong influence on growth and differentiation of tissues such as the brain, muscle and bone, while at the same time stimulating metabolic activity as for example, oxygen consumption, ion transport and nitrogen metabolism (26, 36, 44). Not included are some actions of the hormone on complex processes that are under multi-hormonal control, such as behavioural responses to photoperiodicity in birds or the migratory movements in fish.

In view of the broad spectrum of physiological functions of TH mentioned above, it comes as no surprise that a wide variety of biochemical processes have been implicated over the last 50 years as constituting the mechanism underlying the physiological actions, some of which are presented in Table II. These are arbitrarily divided as rapid and slow responses, although it should be realised that there is no sharp temporal boundary separating these (34, 44, 49). Some responses to TH, such as the regulation of movement of ions, sugars and amino acids, are too rapid be explained as the consequence of the hormonal control of RNA and protein synthesis. On the other hand, many « metabolic » actions at the tissue and cellular levels, such as respiration, ATPase activity, nitrogen metabolism, etc., are dependent on transcriptional control. Indeed, effects of TH on chromatin structure and transcription are among the most rapid responses of target tissues and inhibition of transcriptional activity is known to block not only the growth and developmental actions but many metabolic processes regulated by TH (44, 49). With the discovery that thyroid hormone receptor (TR) is a member of the nuclear steroid/thyroid hormone supergene family (5, 31, 49), and that the dynamics of transcriptional stimulation and receptor occupancy in the nucleus are very intimately linked in vivo (33), TR now occupies a central position in our thinking about the mechanism of thyroid hormone action. 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 thyroid hormone receptors (TRs) are highly conserved and it is generally accepted that the primary intracellular event is the interaction between TR and its ligand in the cell.

Table I: Some of the multiple physiological actions of thyroid hormone
Tableau I : Quelques unes des multiples actions physiologiques de la thyroïde.

<table>
<thead>
<tr>
<th>Species</th>
<th>Growth and development</th>
<th>Metabolic effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mammals, birds</td>
<td>Rate of overall body growth</td>
<td>Regulation of basal metabolic rate and cardiac activity</td>
</tr>
<tr>
<td>Amphibia</td>
<td>Morphogenesis, tissue re-modelling and cell death at metamorphosis</td>
<td>Movement of water and ions across epithelial cells</td>
</tr>
<tr>
<td>Most vertebrates</td>
<td>Maturation of central nervous system and bones</td>
<td>Regulation of water and ion transport, Ca²⁺, nitrogen, fat and cholesterol metabolism</td>
</tr>
<tr>
<td></td>
<td>Proliferation of cellular membranes and structures</td>
<td></td>
</tr>
</tbody>
</table>

Table II: Relatively rapid and slow biochemical responses to thyroid hormone.
Tableau II : Réponses biochimiques relativement rapides et lentes à l’hormone thyroïdienne.

<table>
<thead>
<tr>
<th></th>
<th>Rapid</th>
<th>Slow</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enhanced movement of ions, amino acids, sugars, etc.</td>
<td>Accelerated accumulation of total cellular RNA</td>
<td></td>
</tr>
<tr>
<td>Re-organization of chromatin structure and composition</td>
<td>Higher overall RNA polymerase activities</td>
<td></td>
</tr>
<tr>
<td>Small increase in RNA Polymerase II activity in vitro</td>
<td>Enhanced accumulation of polyribosomes</td>
<td></td>
</tr>
<tr>
<td>Small increase in amino acid incorporation in vivo</td>
<td>Enhanced overall protein synthesis in vitro</td>
<td></td>
</tr>
<tr>
<td>Increased synthesis of ornithine decarboxylase and polyamines</td>
<td>Increased synthesis of Na⁺/K⁺ - ATPase</td>
<td></td>
</tr>
</tbody>
</table>
nucleus and that the diversity of actions of TH is generated by species- and tissue-specific factors and mechanisms.

Whereas the developmental, growth-promoting and metabolic actions of TH in postnatal and adult mammals can be analyzed experimentally with some degree of precision the same is not possible for determining the role of the hormone in postembryonic and foetal development. The major reason for this obstacle lies in the transplacental transfer of TH to the developing mammalian organism and the multiple and complex interplay between thyroid and other hormones and growth factors during intrauterine development (3, 14). It is therefore necessary to examine the developmental actions of TH in organisms in which fertilization occurs externally and the embryos are free-living. The obligatory requirement of thyroid hormone for amphibian metamorphosis, and its many similarities with mammalian postembryonic development, therefore, offers an ideal model to explore its developmental actions in vertebrates (16, 17, 48).

Table III: Diversity of morphological and biochemical responses to thyroid hormone during amphibian metamorphosis.

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Morphological</th>
<th>Biochemical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain</td>
<td>Re-structuring; axon guidance and growth; cell turnover</td>
<td>Cell division; apoptosis; protein synthesis</td>
</tr>
<tr>
<td>Liver</td>
<td>Functional differentiation; re-structuring</td>
<td>Induction of albumin and urea cycle enzymes; larval adult haemoglobin switch</td>
</tr>
<tr>
<td>Eye</td>
<td>Re-positioning; new retinal neurones; altered lens</td>
<td>Visual pigment switch; induction of β-crystallin</td>
</tr>
<tr>
<td>Skin</td>
<td>Re-structuring; keratinisation; granular gland formation</td>
<td>Induction of collagen, 63 kDa keratin, magainin</td>
</tr>
<tr>
<td>Limb bud, lung</td>
<td>De novo morphogenesis of bone, skin, muscle, nerve, etc.</td>
<td>Cell proliferation; gene expression</td>
</tr>
<tr>
<td>Tail, gills</td>
<td>Total tissue regression and removal</td>
<td>Programmed cell death; induction of lytic enzymes</td>
</tr>
<tr>
<td>Intestine, pancreas</td>
<td>Major re-modelling of tissues</td>
<td>New structural and functional constituents</td>
</tr>
<tr>
<td>Immune system</td>
<td>Re-distribution of immune cell populations</td>
<td>Acquisition of new immunocompetence</td>
</tr>
<tr>
<td>Muscle</td>
<td>Growth, differentiation, apoptosis</td>
<td>Induction of myosin heavy chain</td>
</tr>
</tbody>
</table>

AMPHIBIAN METAMORPHOSIS

Following the discovery by Gudernatsch in 1912 (19) 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 T₄, confirmed that the process of metamorphosis was obligatorily dependent on thyroid hormone. By the 1950s much evidence had accumulated to show that the hormone provokes diverse and multiple morphological, physiological and biochemical responses in virtually every tissue of the amphibian tadpole (12, 53). Table III lists some of the important responses to TH in different tissues of the pre-metamorphic tadpole, which range for example from de novo morphogenesis, re-patterning, functional re-programming and partial and total regression of most tissues. Before extending this article to the biochemical and molecular mechanisms underlying the developmental actions of thyroid hormone, it is useful to briefly consider the special characteristics of the role of TH in amphibian metamorphosis.

The thyroidectomized anuran larva will continue to grow without it undergoing metamorphosis, and thus not acquiring the adult phenotype. Administration of T₄ or T₃ at any stage after thyroidectomy will cause the resumption of the arrested differentiation and lead to metamorphosis, which clearly establishes the obligatory requirement of TH for this postembryonic developmental process. It also indicates that the genetic programme for post-embryonic development is stable and not determined temporally. The competence for metamorphosis is established well before the tadpole’s thyroid gland has developed functionally (43), which must mean that TH receptor is 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 (21, 42). In a study in which the tail and limb buds from the same tadpole were cultured in parallel, T₃ induced morphogenesis in one tissue but cell death in the other, thus demonstrating that the hormone initiates diametrically opposite developmental changes in these two tissues.

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 environ-

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mentally transmitted signals can modify the response of a given tissue to TH. Among important endocrine factors are glucocorticoid hormone, CRF (corticotrophin-releasing hormone) and prolactin (PRL) (fig. 1). Exogenous glucocorticoids, ACTH and CRF are known to potentiate, while PRL blocks both natural and TH-induced metamorphosis in whole tadpoles and organ cultures (24, 47). The modulation of TH action by glucocorticoids and PRL has provided a useful tool in analyzing the action of TH, especially in organ cultures of tadpole tissues.

Table III illustrates that no two tissues of the amphibian larva exhibit the same response to TH. Some of the responses 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 (48). As shown in fig. 2, the stimulation of transcription is one of the earliest biochemical responses of a *Xenopus* tadpole tissue to exogenous T₃ (49). Furthermore, blocking the stimulation of transcription will prevent most of the downstream biochemical and physiological responses to TH (42). 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 their colleagues have been able to classify genes in *Xenopus* tadpoles which are up- or down-regulated by T₃ and those that are direct response genes (40). Most direct response genes are up-regulated during metamorphosis, even in tissues programmed for total tissue regression.

A major characteristic of metamorphosis is the restructuring and further differentiation of tissues such as the brain, limb buds, intestine and pancreas (46). 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 apoptosis being a common feature of programmed cell death during development.

**THYROID HORMONE RECEPTORS**

Thyroid hormone receptors are the key to understanding how the hormone controls its diverse metabolic and developmental functions, including metamorphosis. The interaction of TH with TRs 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.

**Principal characteristics of thyroid hormone receptors**

TRs are members of an evolutionarily highly conserved superfamilly of steroid/thyroid hormone/retinoid nuclear receptors that function as ligand-inducible transcription factors (2, 5, 27, 31, 56). In all vertebrates they are encoded by two genes termed TRa and TRb 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

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**Figure 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 T₄ and T₃ 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, corticotrophin-releasing factor; TSH, thyroid stimulating hormone; T₄, L-thyroxine; T₃, triiodo-L-thyronine; GC, glucocorticoid hormone.

**Figure 1:** - Réprésentation schématique de la régulation hormonale de la métamorphose amphibienne. La glande thyroïdienne dormante du têtard est activée et produit des hormones T₄ et T₃ suite à la stimulation des hormones hypothalamiques et hypophysaires répondant aux facteurs environnementaux. L’hormone thyroïdienne (TH) est obligatoire pour l’initiation et le maintien de la métamorphose. Son action est favorisée par l’hormone glucocorticoïde et inhibée par la prolactine.
The subgroup that includes nuclear receptors for retinoic and 9-cis retinoic acids (RARs and RXRs, respectively), vitamin D₃ (VDR) and peroxisome proliferators (PPAR) are unliganded TRs are constitutively located in the nucleus as components of chromatin; by combining with TRs, T₃ activates the transcription of its target genes by interacting with thyroid response elements (TREs) in their promoters, the most common motif being AGGTCA 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 (5). 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 (35, 54). It will not be surprising that more components participating in such complexes and structurally organized as chromatin are discovered in the near future.

Developmental regulation of amphibian TRs

In *Xenopus* tadpoles normal metamorphosis does not begin until the larval thyroid gland becomes functional, which can be about 6 weeks after fertilization. The onset and rapid acceleration of metamorphosis correlates well with the build-up of circulating T₃ (45). The fact that competence to respond to exogenous TH is established as early as 1 week after fertilization (43) 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 premetamorphic larvae (11, 48) 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.

AUTOREGULATION OF TRS DURING METAMORPHOSIS

Biochemical, in situ hybridisation 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 re-structuring (40, 47, 48).
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 $\beta$ than the $\alpha$ gene and is the result of direct activation of their transcription (30, 45, 50). The advantage of studying receptor autoinduction in tissue culture is not only a greater precision of 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 (30, 37). These studies also demonstrated that TR-RXR heterodimers, but not TR monomers or homodimers, specifically interacted with TREs in the promoter of the Xenopus TR$\beta$ gene, and that the heterodimer could regulate the transcription of TR.

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 (52). A large number of d-n TRB1 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 (38, 56). It is therefore significant that human mutant TRBs and a synthetic mutant Xenopus TR$\beta$ were able to inhibit autoinduction of wild-type TR$\beta$ 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 (52). More interestingly, based on a previously described technique (9), transfection of tadpole tail muscle in vivo showed that d-n mutant TRs prevented wild-type TR$\beta$ autoinduction in premetamorphic 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. 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.

First, there is a good correlation between the inhibition and potentiation of metamorphosis by PRL and glucocorticoid, respectively, and the inhibition or enhancement of autoinduction of TR and RXR genes in several tadpole tissues during natural or T$_{3}$-induced metamorphosis (1, 22, 50). This correlation is particularly marked for the antagonism between TH and PRL, as can be discerned from Table IV. PRL blocks the upregulation of both TR $\alpha$ and $\beta$ mRNAs induced by T$_{3}$, but does not affect the constitutive expression of the receptor genes in whole 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 premetamorphic Xenopus tadpole tails. The mechanism of the antimetamorphic action of PRL in amphibia remains unknown, although recently some progress has been made in elucidating the molecular action of this hormone in mammals, since its receptor has been identified as a cytokine type of receptor through which the hormonal signal is transduced from the cell membrane to the nucleus via the JAK/STAT pathway (6).

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 spontaneously (39, 50, 55). 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

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Relative TR$\alpha$</th>
<th>Relative TR$\beta$</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>505</td>
<td>24</td>
</tr>
<tr>
<td>T$_{3}$</td>
<td>1290</td>
<td>368</td>
</tr>
<tr>
<td>T$_{3}$ + PRL</td>
<td>799</td>
<td>10</td>
</tr>
<tr>
<td>PRL</td>
<td>405</td>
<td>43</td>
</tr>
</tbody>
</table>

Batches of 20 stage 50 Xenopus tadpoles were treated with 2x10$^{-6}$ MT$_{3}$ 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 IV: - Relative accumulation of TR$\alpha$ and $\beta$ mRNAs in pre-metamorphic Xenopus tadpoles treated with T$_{3}$ and prolactin (PRL).

Tableau IV : - Accumulation relative de $\alpha$-TR et de $\beta$-ARNm dans le têtard prémétamorphique Wenopus traité par T3 et prolactine.
amphibia such as *Necturus* and *Proteus* do not respond to TH. As can be seen in Table V, 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 TR\( a \) transcripts could be detected in tissues of *Necturus* in which \( T_3 \) failed to upregulate the expression of TR\( a \) or b mRNA.

Table V : - Association between TR autoinduction and response to thyroid hormones (\( T_3, T_4 \)) of spontaneously metamorphosing and facultatively or obligatorily neotenic amphibia.

<table>
<thead>
<tr>
<th>Species</th>
<th>Metamorphosis</th>
<th>Endogenous ( T_3, T_4 )</th>
<th>TR Genes</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Expressed*</td>
<td>Autoinduced**</td>
</tr>
<tr>
<td>Xenopus</td>
<td>Spontaneous</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Ambystoma</td>
<td>Facultatively neotenic</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Necturus</td>
<td>Obligatorily neotenic</td>
<td>Yes</td>
<td>Yes</td>
<td>Na</td>
</tr>
</tbody>
</table>

* Only TR\( a \) detectable in *Necturus*
** By exogenous TH

Table VI : - Some examples of mammalian postembryonic developmental expression of genes and processes specifying the adult phenotype.

<table>
<thead>
<tr>
<th>Process</th>
<th>Genes and tissues</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gene switching</td>
<td>( \alpha )-Foetoprotein to albumin and foetal to adult haemoglobin in liver; immunoglobulin genes</td>
</tr>
<tr>
<td>Morphogenesis</td>
<td>Maturation and differentiation of limb, bone, lung, skin</td>
</tr>
<tr>
<td>Neurogenesis</td>
<td>Neural cell turnover, axonal growth, acquisition of new sensory functions</td>
</tr>
<tr>
<td>Tissue re-modelling</td>
<td>Keratinization of epidermis; connective tissue formation; re-structuring of intestine</td>
</tr>
<tr>
<td>New functions</td>
<td>Nitrogen metabolism and urea synthesis; new cell adhesion molecules</td>
</tr>
<tr>
<td>Cell death</td>
<td>Removal of tissues or organs by induction of lytic enzymes and expression of cell death and survival genes; digit formation</td>
</tr>
</tbody>
</table>

RELEVANCE OF AMPHIBIAN METAMORPHOSIS TO MAMMALIAN POSTEMBRYONIC DEVELOPMENT

In contrast to the abrupt changes in response to thyroid hormone observed during amphibian metamorphosis mammalian postembryonic or foetal development is characterized by a relatively slow and more continuous progression of developmental changes at a time when the foetus is exposed to multiple hormonal and other developmental signals of both maternal and foetal origin (3, 7, 14). Nevertheless, there are some remarkable similarities between the developmental changes induced by thyroid hormone during metamorphosis (Table I) and those seen during intrauterine and perinatal development of mammals (Table VI). Good examples of the similarities are the switch from larval or foetal to adult haemoglobin, induction of albumin genes, skin keratinization, bone and limb maturation and the appearance of urea cycle enzymes.

Prominent among the similarities are the parallelism between structural and functional changes that occur in the larval or foetal brain and limb development during amphibian metamorphosis and mid- to late foetal (or perinatal) development in mammals (4, 7, 25, 32, 45), where TH also plays an important role. Perhaps the best documented illustration of the importance of TH during human foetal or perinatal development is cretinism or severe mental retardation and abnormal skeletal differentiation caused by a deficiency of TH at mid- late stages of pregnancy. (8, 10, 28, 34). Experimental hypothyroidism induced in rodents during this period has been shown to cause severe impairment of many sensory functions (taste, hearing, vision). It is therefore of considerable interest, as illustrated in Fig. 3 for human foetal development, that the establishment of these physiologically normal sensory functions is intimately linked with a substantial surge in the level of TH in foetal blood. Tissue culture studies have shown a direct action of TH on the differentiation of several types of neuronal cells involved in a wide range of sensory as well as non-sensory functions (10, 28, 34, 45). Recently Forrest and his colleagues (15) (1996), have demonstrated a deficient hearing ability in mice in which the TR\( b \) gene had been « knocked-out » by homologous recombination. It is therefore most significant that TH exerts a strong influence on olfactory and optical patterning and func-
Figure 3 : Idealized curves illustrating the intimate association between the appearance of thyroid hormone (TH) in human foetal plasma, the proliferation of neuronal (N) and glial (G) cells and the acquisition of different sensory functions (arrows) during peri- and post-natal development. The proliferation of neuronal and glial cells is represented as relative increments of DNA at different times of development.

Figure 3 : Courbes théoriques montrant l’association étroite entre l’apparition de l’hormone thyroïdienne (Th) dans le plasma du fœtus humain, la prolifération des cellules neuronales (N) et gliales (G) et l’acquisition de différentes fonctions sensorielles (flèches) au cours du développement péri et post-natal. La prolifération des cellules neuronales et gliales correspond à une augmentation relative d’ADN à différents moments du développement.

REFERENCES

6. Cleveinger CV, Medaglia MV. The protein tyrosine kinase p59fyn is associated with prolactin (PRL) receptor and is activated by PRL stimulation of T-lymphocytes. Mol Endocrinol 1994; 8: 674-81.
9. De Luze A, Sachs L, Demeine B. Thyroid hormone-dependent transcriptional regulation of exo-


11. Elicett B, Brown DD. Quantitation of endoge-


13. Fairclough L, Tata JR. An immunochemical analysis of thyroid hormone receptor α and β pro-


15. Forrest D, Erway LC, Ng L, Altschuler R, CurrAn T. Thyroid hormone receptor B is essen-


17. Gilbert LI, Tata JR, Atkinson BG (eds). Meta-

18. Gorbman A, Bern HA. A Textbook of Compa-


19. Guder Natsch JP. Feeding experiments on tad-


21. Ishizuka-Oka A, Shimozawa A. Induction of meta-

22. Ishimaru S, Tata JR. Contrasting patterns of ex-
pression of thyroid hormone and retinoid X recep-
tors genes during hormonal manipulation of Xenopus tadpole tail regres-

23. Kanamori A, Brown DD. The regulation of thy-


25. Kondo T, Herault Y, Zakany J, Duboule D. Genetic control of murine limb morphogenesis. Relationships with human syndromes and evolu-


27. LaudeT V, HANNI C, COLL J, CatzeplIS F, StehelinD. Evolution of the nuclear receptor gene superfami-


30. Machuca I, Tata JR. Autoinduction of thyroid hormone receptor during metamorphosis is repro-

31. Mangelsdorf DJ, Evans RM. The RXR heterod-


39. Safi R, Begg A, HANNI C, STEHELID T, Tata JR, LaudeT V. Thyroid hormone receptor genes of neo-


41. Southard JD, Talamanes F. Placental prolactin-like proteins in rodents : variations on a structural theme Molec Cell Endocrinol 1991 ; 79 : C133-

C140.

42. Tata JR. Requirement for RNA and protein syn-


44. Tata JR. Growth and developmental actions of thyroid hormones at the cellular level. In : Handbook of Physiology, Section 7, Endocrinology 3. 1974, pp. 469-78.


47. Tata JR. Homonal interplay and thyroid hormone receptor expression during amphibian metamor-


48. Tata JR. Hormonal signaling and amphibian meta-


50. Tata JR, Kawahara A, Baker BS. Prolactin inhi-
bits both thyroid hormone-induced morphogenesis and cell death in cultured amphibian larval tissues. Dev Biol 1991 ; 146 : 72-80.
52. Ulisse S, Esslemont G, Baker BS, Chatterjee VKK, Tata JR. Dominant-negative mutant thyroid hormone receptors prevent transcription from Xenopus thyroid hormone receptor b gene promoter in response to thyroid hormone in Xenopus tadpoles in vivo. Proc Natl Acad Sci USA 1996; 93: 1205-9.


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