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Review

The road to nuclear receptors of thyroid hormone ☆

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ABSTRACT

Background: Early studies on the mechanism of action of thyroid hormone (TH) measured changes in enzyme activities following the addition of L-thyroxine (T_4) and 3, 3′, 5-triiodothyronine (T_3) to tissue extracts and purified enzymes.
Scope of review: As techniques for isolation of mitochondria, ribosomes, nuclei and chromatin, were increasingly refined, it became possible to study complex cellular processes, such as oxidative phosphorylation, protein synthesis, transcription and chromosomal structure. Uncoupling of oxidative phosphorylation and direct action on protein synthesis as mechanisms of action of TH, proposed in the 1950s and 1960s, were found to be untenable as mechanisms of physiological action because of inappropriate experimental conditions.
Major conclusions: Several findings in the 1960s and 1970s, mainly 1) that near-physiological doses of T_3 stimulated transcription measured in vivo or in nuclei isolated from tissues of rats and frog tadpoles, 2) the inhibition of hormone action by inhibitors of transcription and 3) the rapid and almost identical kinetics of accumulation of labelled hormone and RNA synthesis in target cell nuclei, pointed to the cell nucleus as a major site of its action. The application of technologies of recombinant DNA, gene cloning and DNA sequencing in the mid-1980s allowed the identification and understanding of the structure and function of nuclear receptors of TH.
General significance: This review traces the road leading to the nuclear receptors of thyroid hormone, thus explaining how the hormone influences gene expression. It also illustrates the importance of how new concepts originate from the progression of technological innovations. This article is part of a Special Issue entitled Thyroid hormone signalling.

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1. Introduction

By the second half of the 19th century, physicians had established a credible link between thyroid atrophy and iodine deficiency and diseases such as, goitre, cretinism and myxedema. A few years later, surgeons reported that thyroidectomy led to the development of myxedema and the appearance of symptoms resembling cretinism in their patients. Even more striking was the effect of thyroidectomy on growth in children. By the early 20th century, removal of the gland in experimental animals, and grafting it back to reverse the effects of thyroidectomy, corroborated the beneficial effects of administering ovine, bovine and porcine thyroid powder or extracts for the treatment of patients suffering from myxedema, cretinism and growth retardation or other consequences of thyroid deficiency. A chance observation in 1912 that extracts of mammalian thyroid gland induced metamorphosis precociously in frog tadpoles emphasized the important role of thyroid hormone in regulating post-embryonic growth and development in all vertebrates. For detailed accounts of the early work on thyroid chemistry, physiology and disorders, see Harington [1] and Pitt-Rivers and Tata [2]. As regards the question of the biologically active principle in the thyroid, it was Edward Kendall who, in 1915, identified and worked out the structure of a most novel substance with hormonal activity and which he called thyroxine [3], followed a few years later by the total synthesis of L-thyroxine, by Harington. The availability of a synthetic and chemically pure hormone made it easier for physiologists to quantify biological activity of the hormone in most vertebrate species.

L-Thyroxine (T_4) was considered to be the sole peripherally active thyroid hormone for nearly 30 years until 3,3′, 5-triiodo-L-thyronine (T_3) was discovered simultaneously in rat thyroid and human blood by groups in Paris [4], and London [5], respectively. The London laboratory synthesized T_3 and also showed that much of the T_3 in blood was derived from the partial deiodination of T_4. Soon T_3 was found to be biologically more potent than T_4 in all the assays available. One of the first facts to emerge was that the two molecules were conserved in all species and tissues through evolution, from the most primitive organisms, such as *Amphioxus* to man (see Barrington [6]). In most later studies it was agreed that T_3 is the physiologically active thyroid hormone and that T_4 is its precursor and should be considered as the pro-hormone. The availability of chemically pure T_4 in

Abbreviations: TH, Thyroid hormone; T_4, L-thyroxine; T_3, 3,3′,5-triiodo-L-thyronine; TR, thyroid hormone receptor

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1930, followed 30 years later with that of T_3 and many of their biologically active and inactive analogues, led to several explanations, often mutually incompatible, for the multiple actions of thyroid hormone. In this review I describe how the major thinking on the biochemical and physiological mechanisms underlying the metabolic and growth and developmental properties of the hormone has evolved in parallel with the technical developments at the laboratory bench — progressing from the purification of proteins, enzymology and the close association between protein structure and function. Later, the possibility of studying complex cellular functions, the isolation of sub-cellular components and the consequences of their interaction with TH and other signalling molecules, generated theories based on complex metabolic processes, protein synthesis and transcription. The emergence of technologies of gene cloning, DNA sequencing and cell transfection represented an extraordinary advance leading for the first time to the identification and understanding of structure and function of hormone receptors located both in the cell membrane and nucleus. The account below summarizes the major steps leading to the foundation of our current understanding of the important signalling mechanisms generated by the interaction between TH and its nuclear receptors.

2. Multiple actions of thyroid hormone

What are the messages delivered by the thyroid hormonal signal? As is clearly evident from Table 1, one of the most striking characteristics of the physiological action of TH is its multiplicity, both as compared among different species of organisms or from one tissue to another within the same organism [7]. These are sub-divided in this Table into two groups: a) those that regulate metabolic functions and b) those that control growth and development. The responses to the hormone vary not only according to species or tissue but also according to the developmental stage. Generally, the metabolic responses are most markedly visible in endotherms and which form the basis of the clinical symptoms of hypo- and hyper-thyroidism, often manifested as changes in basal metabolic rate (BMR), water retention, lipid metabolism, etc. The hormonal effects on growth and development are particularly evident in ectotherms, and, albeit to a lesser degree, during the post-embryonic or perinatal period in warm-blooded vertebrates. A particularly dramatic example of the multiple responses to TH is seen when comparing the tissue-specific responses to the hormone during amphibian metamorphosis (see Section 4). No two tissues or groups of cells exhibit the same hormonal responses, which can range from de novo morphogenesis, functional reprogramming and total or partial tissue loss. It raises the important question, when considering receptors, as to whether the multiplicity originates from an initial interaction with a unique cellular element or whether it is the result of separate interactions between the hormone and distinct cellular elements.

Table 1
Multiplicity of biological actions of thyroid hormone.

Growth and developmental actions	Metabolic actions
Rate of postnatal growth of many mammalian and avian tissues	Regulation of basal metabolic rate in homeotherms
Functional and biochemical maturation of foetal brain and bone	Movement of water and Na^+ ions across cell membranes
	Calcium and phosphorus metabolism
Morphogenesis, gene switching and cell death in amphibian larval metamorphosis	Regulation of metabolism of cholesterol and other lipids
Control of moulting in birds	Nitrogen (urea, creatine) metabolism
Regulation of synthesis of mitochondrial respiratory enzymes and membranes	Control of oxidative phosphorylation and energy metabolism

3. Early biochemical explanations of thyroid hormone action

3.1. Direct interactions

At the beginning of the twentieth century, physiologists and biochemists proposed mechanisms of hormone action that were applicable to all endocrine secretions. But as increasing numbers of pure hormones became available, and as the biochemical and physiological test systems were better defined and quantifiable, there was a move away from a generic or common mechanism of hormone action. The first studies in the 1920s in whole animals following the administration of crude thyroid extracts or the removal of the thyroid gland failed to reveal any clear-cut mechanism of hormonal action in regulation of BMR — a key physiological action in adult mammals and birds. The same was true of overall respiration of tissue slices prepared from hormone-supplemented or -deprived animals, or of individual metabolic or biochemical end-points. Addition of the hormone in vitro to tissue preparations gave ambiguous results, largely because of the very high, supra-physiological amounts of TH or its derivates used. The ready availability of synthetic L-thyroxine in the 1930s, coinciding with the rapid progress in biochemistry, particularly enzymology, in the 1930s and 1940s, led many laboratories in that period to study the direct interactions between TH and a variety of enzymes. Since tissue O_2 consumption was considered by many to be the basis of regulation of BMR by TH, it was logical that most of the direct hormone–enzyme interaction studies involved enzymes with oxidative functions, e.g. dehydrogenases or oxidase complexes [8–10]. Often, the results of adding L-thyroxine to purified enzymes led to inconclusive results, or were mutually contradictory, with little or no bearing on hormonal action under physiological conditions in vivo.

3.2. Uncoupling of oxidative phosphorylation

A major breakthrough in cell biology at the beginning of the 1950s was the feasibility of studying oxidative phosphorylation in isolated mitochondria [11], which account for the bulk of a cell's oxygen consumption and energy production. Many high-profile biochemical research laboratories in the late 1950s and early 1960s were engaged in trying to discover, first, how the 3 molecules of ATP are generated for each electron accepted by oxygen (P:O = 3) in the fully coupled state, and, later [11,12], to discover the identity of a presumed high energy phosphorylated intermediate termed by some as X~P. As the points of entry of electrons from various substrates available to mitochondria were then well established, it was thought by many that TH stimulated BMR by uncoupling oxidative phosphorylation. It was thought that uncoupling would lead to higher oxygen consumption to compensate for the diminished production of ATP. But, when the focus of oxidative phosphorylation shifted towards the identity of the presumed high energy phosphorylated intermediate X~P, there was virtually no agreement among the different laboratories working on this problem, neither as to the nature of the high energy intermediate nor that of the enzymes thought to be involved in its formation. Eventually, the whole concept of a high-energy intermediate was abandoned when Mitchell published his chemiosmotic theory of oxidative phosphorylation [12].

One of the principal reasons for the abandonment of theories of mechanism of action of TH, based on uncoupling of oxidative phosphorylation, was that the experimental biochemical conditions failed to take into account those governing the physiology of hormone action. To cite a few discrepancies, a) the amount of TH administered in vivo or added to isolated mitochondria or other preparations was several hundred, or even thousand, times what would correspond to "physiological", i.e. the quantities used reflected its toxicity; b) biologically inactive analogues of TH often gave the same results as T_4 and T_3; and c) the effects were often very rapid and ignored the long latent period preceding the physiological response in vivo. The

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