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fortunately, this article cannot be easily refuted, more for its source than its value compared to other ignored landmark papers.

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MAIN CONCLUSION: Pituitary makes its own T3, so when it makes TSH, the level may not reflect the level needed by tissues that can't make T3 or do it diffferently

Iodine Landmark Paper: Pituitary Nuclear 3,5,3′-Triiodothyronine and Thyrotropin Secretion: An Explanation for the Effect of Thyroxine

if a critter or toxin stimulates T3 receptors in the hypothalamus or pituitary, it can impair the entire body's defense !!

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BACKGROUND

Iodine is an essential component of thyroid hormones. The thyroglobulin-derived iodothyronine molecules contain 3 or 4 iodine atoms that are covalently bound during iodide organification. This process, also known as iodination, is catalyzed by thyroid peroxidase and requires that the thyroid cell concentrate iodide from plasma. Iodine is readily available from the ocean, and salt-water vertebrates, the first life forms to develop a thyroid gland, are not at risk for iodine deficiency. However, in terrestrial vertebrates, including humans, iodine availability can be limiting depending on the proximity to the ocean and the iodine content of the soil.

even water-based organisms store up iodine as thyroid

Iodine content and structural localization in various thyroid products determine the biological potency of thyroid secretions. As an example, the prohormone 3,3′,5,5′-tetraiodothyronine (T4), which contains 4 iodine atoms, must undergo outer-ring monodeiodination to 3,3′,5-triiodothyronine (T3) in order to achieve its full biological potency. This process is catalyzed primarily by the type 1 5′-deiodinase (D1), a propylthiuracyl (PTU) sensitive enzyme expressed in most tissues [1].

While the role of iodine in thyroid hormone action and metabolism has long been known, the critical role of another trace element featured in this Landmark issue, selenium, only came to light over the last dozen years. Nutritional studies in animals had implicated a role for selenium in thyroid hormone metabolism in the late 1980′s. Arthur, Beckett and colleagues found that rats maintained on a selenium-deficient diet for 4–6 weeks had elevated levels of serum T4 and decreased serum T3 compared to their selenium-sufficient counterparts [2]. Time course studies showed these changes to be progressive with increasing deficiency [3], leading these investigators to propose a direct role for selenium in thyroid hormone metabolism.

low Se impairs conversion from T4 to T3, as well as higher risks for Hashi and thyroid cancer

At about the same time, studies in regions in Africa with overlapping iodine and selenium deficiency implicated selenium in thyroid function in humans. In areas of severe iodine deficiency, myxoedematous cretinism, characterized by early onset hypothyroidism and absence of goiter, is prevalent [4,5]. Certain areas with severe

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iodine deficiency are also characterized by selenium deficient soil, and low glutathione peroxidase activity in residents. Selenium supplementation in these regions was found to produce a further decline in the already low T4 levels, and supplementation trials were therefore halted until iodine sufficiency could be established.

giving Se without I has pitfalls!

These findings were explained upon cloning of the first iodothyronine deiodinase enzyme, D1. These studies revealed that D1 contained the unusual amino acid, selenocysteine, in the active site [6]. The critical role for selenocysteine in deiodinase function was subsequently shown through mutagenesis studies [7]. Eventual cloning of the type 2 and 3 deiodinases (D2 and D3 respectively) revealed that they are also selenoenzymes [8,9], further establishing the critical role of one trace element, selenium, in the metabolism and function of another, iodine.

The target cells of thyroid secretion contain thyroid receptors (TR). These are high affinity nuclear T3 binding proteins that have little affinity for T4. Therefore, T4 to T3 conversion, a process catalyzed by D1 and D2, is the essential first step in thyroid hormone action. D3, on the other hand, inactivates T4 and T3 by inner-ring deiodination and, as discussed below, functions to fine-tune the levels of exposure of certain tissues to circulating thyroid hormone. As a group, these enzymes constitute a powerful mechanism regulating the thyroid status of vertebrates.

deactivates T4 and T3
BUT
provides an iodide atom to do other things!

thyroid levels have strong epigenetic effects!

TR regulates transcription of thyroid-dependent genes and hence multiple biological processes, including cell differentiation, growth and energy expenditure. In the case of genes that are positively regulated by T3, there is evidence that empty TR molecules interact with cis-acting elements in the target gene (TRE) and also with nuclear factors known as corepressors, suppressing gene activity. However, in the presence of T3, T3-TR complexes are formed which can also bind to TRE. These complexes trade the partnership with corepressors for an association with coactivators that eventually will activate gene transcription. It is assumed that the opposite occurs with genes that are negatively regulated by T3 [10].

Even though in the mid-seventies much less was known about the molecular mechanisms involved in T3 action, it was clear that the nucleus was the site of initiation of thyroid hormone action and that the level of T3-TR complexes in the nucleus was critical for the thyroid impact on biological processes [11]. Based on the fact that TR occupancy is determined by receptor affinity for T3 and the nuclear concentration of T3, which is in equilibrium with plasma T3, a dogma was developed that plasma T3 is the main, if not the only, source of nuclear T3. This is certainly the case in tissues such as liver and kidney, where the quantity of nuclear T3 and the degree of occupancy of TR can be calculated from the plasma T3 concentration and the nuclear/plasma ratio of tracer T3 at equilibrium. However, a predicted consequence of this generalization is that, based on experimental data, TR saturation in all tissues would be 40–50% and, more importantly, all tissues would be equally affected by changes in plasma T3 concentration. Clinically, all tissues from hyperthyroid patients would be similarly affected by thyrotoxicosis and the opposite would occur in patients with hypothyroidism.

pointing out the existing generalizations (incorrect) that have impeded advancements in treatment (often provided by holisitic docs!)

However, one key finding by the Larsen group [12] set in motion a series of studies that would modify the idea that plasma T3 is the only source of nuclear T3. Administration of T4 to hypothyroid rats resulted in acute inhibition of thyrotropin (TSH) secretion, as rapidly and to the same degree as did T3. Interestingly, the plasma T3 concentration of T4-injected rats increased only minimally, contrasting with the sharp

TSH in rats responds equally to T3 and T4

elevation in the animals injected with T3. Pretreatment with PTU, a D1 inhibitor, did not block the TSH-suppressive effect of T4. Therefore, the T4-mediated TSH suppression could not be explained by—transformation to T3—a subsequent elevation in plasma T3.

Further studies indicated that in some tissues, namely pituitary gland, brain and brown adipose tissue (BAT), there is an additional source of T3 contributed by intracellular T4 to T3 conversion within the tissue, via D2 [13,14]. It was also found that the T3 generated by D2-catalyzed T4 deiodination supplements that from plasma as though it derived from a kinetically different pool. In these tissues, TR saturation is much higher (70–90%) and 50-80% of this T3 is locally produced. Later, these differences were confirmed using constant infusions of tracer T3 and T4 [15] and direct gravimetric determination of nuclear T3 by RIA [16]. These findings, originally described by Silva & Larsen [17], changed the way we understand the mechanism of action of thyroid hormone and elucidated many of the adaptive mechanisms for regulating T3 concentrations in the brain during hypothyroidism or iodine deficiency [18]. It also explained details of the thyroid-pituitary feed-back mechanisms [19] and thyroid-dependent survival during cold exposure [20].

many cells convert T4 to T3 inside, not synced with the blood levels. Up to 80% of T3 is produced locally.

THE LANDMARK PAPER

The studies contained in this paper include the development of new techniques that allowed measurement and identification of the sources of pituitary nuclear T3. These findings also triggered the discovery of D2 and its role in local T3 production. To calculate the plasma T3 contribution to pituitary nuclear T3, hypothyroid rats were acutely treated with T3 mixed with tracer amounts of 125I-T3. Animals were killed at various time-points after the injections to obtain measurements of plasma TSH, T3 and 125I-T3, as well as pituitary nuclear 125I-T3. Based on the nuclear/plasma ratio of tracer T3 and the plasma T3 concentration at the equilibrium time-point they calculated pituitary nuclear T3 (Fig. 1 of the original article). However, it is important to realize that several steps involved in the performance of such experiments represented technical challenges to the investigators. A prime example was the preparation of nuclei from single pituitaries and subsequent analysis in paper chromatography of the butanol:ammonia extracts. The results obtained indicated that there was a remarkable inverse correlation between nuclear occupancy and plasma TSH concentrations.

Next, using similar techniques and calculations, the authors undertook the challenge to measure the pituitary nuclear 125I-T3 after injection of 125I-T4. Their ability to assess what today is referred to as T3(T4), the fraction of nuclear T3 derived from intracellular T4 conversion, is the core of the paper. Surprisingly, during the course of the experiments 30 to 35% of the total pituitary radioactivity was found in the nucleus. Chromatographic analysis further showed that more than 90% of this was due to 125I-T3. More importantly, the amount of T3 present in the nucleus was not different from that in animals injected with T3. One technical problem had to be worked out, however. The investigators needed to measure and discount the amount of plasma 125I-T3 originated as a contamination of the 125I-T4 and that generated via D1 in other tissues. This is a critical point because such contribution would certainly overestimate the T4-derived pituitary nuclear T3. Because D1 activity is decreased during hypothyroidism such levels, however, were very low and could not be mea-

sured by direct paper chromatography. Therefore, they used affinity chromatography with specific T3 antibody conjugated to Sepharose, a much more sensitive method. The authors also controlled for a possible T3 transport facilitation into the nucleus by T4. Animals were injected with 125I-T3 alone or 125I-T3 plus T4, and the amount of 125I-T3 found in the pituitary nuclei was similar in both situations. These very complex techniques developed in this paper were later used to measure TR occupancy in brain [21] and brown adipose tissue [14].

CONCLUSIONS

The findings described in this paper led the way for the discovery of D2 and its role in the local production and regulation of tissue T3 concentration. This is particularly relevant in the light of the subsequent findings that D2 activity increases during hypothyroidism and is suppressed in hyperthyroidism, while the opposite is observed in D3 activity [18].

The importance of local T3 production in the pituitary, cerebral cortex and the brown adipose tissue, and the capacity for D2 to increase and D3 to decrease when serum T4 falls, suggest an important coordinated defense mechanism. In fact, during hypothyroidism, there is an increase in D2 activity in various regions of the CNS while the opposite is observed for D3 mRNA levels. Such compensation would maintain a relatively constant T3 concentration in these tissues even when serum T4 falls 5–10 fold. On the other hand, during hyperthyroidism this mechanism could protect the brain from thyrotoxicity, by decreasing D2 and increasing D3 activities. In some circumstances, such a mechanism could act to defend even the plasma T3 concentration since, in the hypothyroid adult and especially the neonatal rat, extra-thyroidal T3 production occurs via a PTU-insensitive D2 process [22].

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