ROLE OF THE PITUITARY IODOOTHYRONINE 5'DEIODINASE ACTIVITY IN THE NEGATIVE FEEDBACK BY THYROID HORMONE UPON TSH RELEASE

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It is widely accepted that triiodothyronine (T3) accounts for nearly all of the thyromimetic potency of thyroidal secretion. The nuclear thyroid hormone receptors bind T3 with > 10-fold higher affinity than thyroxine (T4), and the intracellular concentration of T4 is not enough to occupy more than 10% of these receptors—a substantial fraction of which may actually be non-specifically bound. About a decade ago, this and the relatively rapid exchange of plasma T3 with the receptor, led to the concept that the thyroid status of the tissues was closely reflected by the plasma concentration of T3 (1).

There was, however, one conspicuous exception. In a number of conditions, experimental as well as clinical, TSH was elevated in spite of normal plasma T3 levels. For example, in experimental iodine deficiency, serum TSH rises promptly after placing the animals on the iodine-deficient diet, yet the plasma T3 remains normal (2), unless the deficiency is extreme and prolonged. Patients in early stages of thyroid gland insufficiency exhibit elevated serum TSH levels with T3 well within normal limits. In both patients and iodine-deficient rats, tissue hypothyroidism is barely evident or simply inapparent, consistent with the concept that the availability of T3 for most tissues depended largely on plasma T3 (3). Only the pituitary gland is evidently hypothyroid, as reflected by the elevation in TSH (2). The reduced plasma T4 in these conditions appeared as the driving force in the elevation of TSH.

These findings could be explained in a number of ways: 1) the suppression of TSH could be mediated by mechanisms different from the other effects of thyroid hormone, i.e., other than via the nuclear receptors, with T4 being as active as, or more active than, T3; 2) there could be previously unrecognized nuclear T4 receptors in the pituitary; and 3) there could be intrapituitary T3 generation and plasma T4 could be a rate-limiting factor. Two pieces of evidence favored either the first or the second explanation. One was the failure to demonstrate T3 generation in pituitary homogenates by Galton (4) and, the other, the observation by Larsen and Frumess that propylthiouracil (PTU) did not prevent the acute T4-mediated inhibition of TSH release (5).

The first experiments performed to explore this seemingly unique effect of T4 on the thyrotrophs addressed the question as to whether or not the T3-induced TSH release inhibition was mediated by the nuclear receptors. The
results of these experiments showed that the acute inhibition of TSH release after a single injection of T3 to hypothyroid rats correlates chronologically and quantitatively with the T3 specifically bound to the nuclear receptors (6), and that the inhibition after various doses of T3 is linearly related to nuclear occupancy (7). Along with the earlier observations that the inhibition of protein synthesis by cycloheximide or actinomycin D prevented the suppressive effects of T3 upon TSH, these results suggested that this effect of T3 was not different from other effects of the hormone, but the T4 inhibition of TSH release could still be mediated by other mechanisms.

Although cytoplasmic pituitary proteins can bind T3 and T4 in a saturable fashion (8), because of their low affinity for T4, these binding proteins do not appear to be receptors; so, other than the weak binding of T4 to the nuclear T3 receptors, no binding sites qualifying as receptors for T4 appeared to be present in the pituitary. When we examined the nuclei of the pituitary cells for T4 binding after injecting tracer amounts of radioactive T4 into euthyroid rats, we only found radioactive T3 bound to these nuclei (9). Most importantly, the radioactively labeled T3 found in the nuclei was specifically bound to the nuclear receptors and could not be accounted for by the minute amounts of radioactive plasma T3 present under those experimental conditions (6,7). In those and subsequent experiments, the nuclear to plasma ratio of 125I-T3 [T4] shortly after the injection of 125I-T4 and 131I-T3 exceeded the nuclear to plasma ratio of 131I-T3 [T3] by a factor of 2-3, indicating rapid and active intrapituitary T4 to T3 conversion (6,7,9). When TSH suppression after T4 was examined in hypothyroid rats, the time course and the extent of the suppression could be closely related to the T3 [T4] found specifically bound to the nuclear receptors (6,7).

Only in the pituitary gland, but not in liver or kidney, did the simultaneous administration of T3 and T4 result in significantly larger amounts of T3 than after the same doses of T3 alone (7), and the simultaneous administration of submaximal doses of T4 and T3 resulted in additive TSH suppression without higher levels of plasma T3 than after the T3 alone (7). Radioisotopic kinetic analyses with pulse injections of 125I-T4 and 131I-T3 (9), and subsequently by constant infusion by van Doorn et al. (10) or by isotopic equilibrium by Obregon et al. (11), indicate that in euthyroid rats the T3 nuclear receptors are about 80% saturated, and that about half of this T3 derives from local (intrapituitary) production. That at physiological doses of T4 all, or nearly all, of the suppressive effect of T4 on TSH was due to the T3 generated in the pituitary was demonstrated by the observation that iopanoic acid, a competitive inhibitor of T4 to T3 conversion, prevented the effect of T4 on TSH, but not that of T3 (12). Although basically indirect, all of this evidence suggested that the apparently unique effect of T4 on TSH release was due to intrapituitary T3 generation with subsequent binding of the T3 [T4] to the nuclear receptors, and to the fact that the latter constituted about 50% of the nuclear T3.

Thus, pituitary 5'deiodination of T4 seems to play a crucial role in determining the physiological characteristics of the feedback of thyroid hormones on TSH secretion. I will now discuss briefly some characteristics of the pituitary 5'deiodinase activity. Before the experiments described above, Larsen and Frumess had found that PTU did not prevent the acute inhibition of TSH by a single replacement dose of T4, and that in thyroidectomized rats maintained on T4, the concomitant administration of PTU reduced plasma T3 levels by 60-70%, prevented the normalization of the thyroid hormone-dependent hepatic alpha-glycerophosphate dehydrogenase, but barely affected the suppression of TSH by the replacement with T4 (5). In light of the experiments described above, these results strongly suggest that pituitary T4 5'deiodination is PTU-sensitive. In vivo studies demonstrated that the quantity of T3 specifically bound to the pituitary nuclei after T4 was not affected by pretreatment with PTU (7). Experiments with pituitary