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# Influence of type II 5' deiodinase on TSH content in diabetic rats

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The influence of hypothalamic and pituitary type II 5'deiodinase (5'D-II) activities and T3 content on pituitary TSH content was investigated in streptozotocin (STZ)-induced diabetic rats (D). The results show, first, that hypothalamic and pituitary 5'D-II activities were lower in neonatal D rats versus control (C) rats, and the normal developmental pattern was altered. Secondly, when D and C rats were thyroidectomized (Tx) at 25 days of age (D+Tx, C+Tx), pituitary and hypothalamic 5'D-II activities increased ten days later in both populations *vs.* intact rats, but the percentage of increase was smaller in D+Tx than in C+Tx. The hypothalamic T3 to T4 ratios were also decreased in D+Tx animals (0.38) as compared to C+Tx rats (1.64). The hypothalamic T3 content was reduced by 30% in D as compared to C rats and by 80% in D+Tx as compared to C+Tx rats, showing a defect in hypothalamic T4 deiodination. Pituitary TSH content increased after Tx in D+Tx, but not in C+Tx. These results in diabetic rats indicate that the hypothalamic and pituitary 5'D-II activity and hypothalamic T3 content are affected by diabetes and play a role in the regulation of pituitary TSH content.

**Key words:** Diabetes, Deiodination, TSH.

Alterations in thyroid function in patients with nonthyroidal illnesses have been widely reported (28, 40). Among all "euthyroid sick syndromes", undernutrition and diabetes show a common pattern at the cellular level: cell starvation due to the lack of nutrients or to their reduced utilization by the absence of insulin. Both,

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undernutrition and diabetes, considered as "low T3 syndromes", induce a significant reduction of serum T3 and T4, together with a fall in pituitary and plasma TSH (1, 13, 26, 30, 34) as opposed to the usual increase in plasma TSH observed in hypothyroidism. Pituitary α and β TSH and GH mRNA levels are decreased in restricted feeding, fasting and diabetes in rats (29). These alterations in the regulation of the thyroid axis are similar in both syndromes, but several differences have also been established. The hepatic T4 to T3 conversion is impaired in diabetes and fasting (1, 2, 12, 24, 25, 27, 34). Diabetes induces a different adaptive pattern at the neuroendocrine level with a reduced hypothalamic TRH content (13) and release (7, 30) as compared to undernutrition (26).

Pituitary and plasma TSH levels depend mostly on the balance between hypothalamic thyroid-releasing hormone (TRH) stimulation and thyroid hormone inhibition at the pituitary level among other factors such as somatostatin and dopamine. However, the reduction in 5' deiodination observed in liver and other tissues from diabetic animals (12, 24, 25, 34), was not found in brain (11, 25) or pituitary (34). So, further research is needed on the role of local conversion of T4 to T3 in pituitary and hypothalamus, a fact that might be important on the regulation of pituitary TSH content and release (18).

Outer ring 5'deiodination (5'D) is catalyzed by two enzymes: type I 5'deiodinase (5'D-I), that provides most of the plasma T3 in rat, and type II 5'deiodinase (5'D-II) found in pituitary, brain, brown adipose tissue, and other organs that is an intracellular source of T3 and it is insensitive to inhibition by 2N-propyl-6-thiouracil (PTU) (16, 21). The 5'D-II plays an important role in the regulation of the T3 concentrations in brain and pituitary. The contribution of local T3 production is much greater in the anterior pituitary gland than in the liver, kidney or muscle (35). Cerebro-cortical 5'D-II levels increase 5-fold 24 h after Tx (20). The local T4 5' deiodination to T3 is crucial for the saturation of nuclear T3 receptors in the anterior pituitary gland and the brain (36). Moreover, T4 must be converted to T3 to produce its full biological effects on pituitary TSH secretion (17, 22). High expression of 5'D-II mRNA is found in the median eminence of the hypothalamus (14, 39). The 5'D-II mRNA levels are also greatly increased in pituitaries from hypothyroid rats (39) suggesting a preferential location of 5'D-II in the thyrotrophs, a cell population that increases after Tx. All this highlights the important role of 5'D-II in the regulation of T3 levels in pituitary and hypothalamus, relative to its feed-back action on TSH secretion. However, the role of T4 deiodination in the regulation of the hypothalamic-pituitary function in diabetes has not been examined, especially at early stages of development when thyroid hormones are crucial for brain development. Most of the T3 in the fetal and neonatal brain is derived from T4 via 5'D-II (8, 9, 23, 37).

Insulin treatment in diabetes is often not enough to restore altered thyroid hormone metabolism in tissues (3, 34). Although the role of insulin in thyroid hormone alterations is thought to be related to the reversal of altered glucose utilization (12), there is an intrinsic pituitary abnormality in uncontrolled diabetic patients that requires further investigation (40). We have previously suggested that the hypothalamic and pituitary 5'D-II activities and T3 concentrations seem to play an important role in the regulation of

the pituitary content and plasma levels of TSH in rats undernourished from gestation (26). Whether the same regulatory pathway takes place in diabetic animals remains to be studied.

We now study the alterations in pituitary and hypothalamic 5'D-II activity in neonatal diabetic rats, comparing the results with those found in undernourished rats (26). In the second part, a study on thyroidectomized diabetic rats (Tx D) is described, to understand the functional role of hypothalamic and pituitary 5'D-II activities and T3 content in the regulation of circulating TSH.

## Material and Methods

*Animals, treatment and experimental design.*– Wistar rats bred in our laboratory under conditions of controlled temperature and artificial dark-light cycle (from 07:00 h to 19:00 h) were used throughout the study. Animals were fed a standard laboratory diet and water *ad libitum*. The number of pups in each litter was evened out to 8. Diabetes was induced at 3 days of life (neonatal rats, *experiment 1*) or at 23 days of life (adult rats, *experiment 2*), by a single intraperitoneal (i. p.) injection of STZ (100 mg/kg body weight) in citrate buffer 0.05 M pH=4.5. Control rats (C) were injected with citrate buffer. Glycemia and serum insulin were determined in order to ensure diabetes had been induced. In the *experiment 1*, samples were taken at 8, 14 and 23 days of life, in both populations of C and diabetic (D) neonatal rats. In *experiment 2*, C and D rats, were thyroidectomized (Tx) at 25 days of life and later received an i.p. injection of 100 µCi $^{131}$I. These animals were killed 10 and 20 days after Tx (35 and 45 days of life) at the same hour to avoid fluctuations in plasma TSH. Plasma was collected and pituitary and hypothalamus were dissected, quickly frozen on dry ice and kept at -80°C for thyroid hormone determination. All studies were conducted in accordance with the principles and procedures outlined in the NIH Guidelines for Care and Use of Experimental Animals and in the protocols and guidelines approved by our institution.

*Drugs and reagents.*– STZ was a kind gift of Upjohn Co. (Kalamazoo, MI). High specific activity ($^{125}$I) T3, ($^{125}$I) T4, ($^{131}$I) T4 and ($^{125}$I) rT3 (3000 µCi/µg) were synthesized in our laboratory using chloramine T, and iodothyronines of a lower iodination level as substrates, as described (5). ($^{125}$I) T3 and ($^{125}$I) T4 were used for the determination of thyroid hormone concentrations, using highly sensitive T4 and T3 radioimmunoassays (RIAs) (5). ($^{131}$I) T4 and ($^{125}$I) T3 were used as recovery tracers during plasma and tissue extractions and ($^{125}$I) rT3 as substrate for 5'deiodinase determinations.

*Determinations.*– Glucose was measured in supernatants of $Ba(OH)_2$-$ZnSO_4$ deproteinized blood by a glucose oxidase method (Boehringer Mannheim, FRG). Serum immunoreactive insulin was determined with purified rat insulin as standard (NOVO, Denmark), antibody to porcine insulin, which cross-reacted similarly with pork and rat insulin standards, and monoiodinated $^{125}$I-labeled human insulin. Charcoal was used to separate free from bound hormone, a method that allows the determination of 6 µU/ml (0.25 ng/ml) with a coefficient of variation within and between assays of 10%.

Pituitary and plasma TSH were measured by RIA using immunoreactants kindly supplied by the Rat Pituitary Agency of the NIDDK, NIH (Bethesda,

MD). Coefficient of variation for this assay is about 10 %. Results are expressed in weight equivalents of the NIDDK rat TSH RP-2 reference preparation.

Iodothyronine type II 5'deiodinase (5'D-II) activity was assayed in pituitary and hypothalamic homogenates as previously described (26). Thyroid hormone concentrations were determined by RIAs, as previously described (26), after extraction and purification of tissues. Hypothalami were pooled in groups of 4 to 6, depending on the size and age of the rat. The limits of detection were 2.5 pg T4 and 0.7 pg T3/tube. Cross reactivities for T4 RIA and T3 RIA were as reported (32).

*Statistical analysis.*– Mean values (±SE) are given. Statistical comparisons were performed by analysis of variance followed by the protected least significant difference test (38).

## Results

*Experiment 1.*– Body weight (BW) increased gradually from 8 to 23 days of life both in control (from 14.4 ± 0.6 g to 52.1 ± 2.2 g; n=9) and diabetic rats (from 10.9 ± 0.4 g to 43.8 ± 1.0 g; n=10). Although STZ was given on the 3rd day of life, a significant decrease in BW in D rats was observed only at day 23 of life. Hyperglycemia was observed in all D rats and insulinemia was significantly lower in the D rats at 14 and 23 days (Table I).

Pituitary 5'D-II activity increased in C rats up to 23 days of life, as previously reported (26) and diabetes decreased pituitary 5'D-II activities by more than 50% (Table I). Hypothalamic 5'D-II activity did not change in C rats along time during the first 3 weeks of age, being the values in D rats significantly decreased at 8 and 14 days. Hypothalamic and pituitary 5'D-II increased in D rats between 8 and 14 days of age.

*Experiment 2.*- The increase of BW between 35 and 45 days in C rats (from 79.2±2.8 g to 130.8±8.5 g), was higher than in C+Tx rats (from 73.7±1.4 g up to 90.7±4.8 g). Also Bw increased in the intact D rats (from 52.8±3.9 g up to 84.5±4.6 g), but not in Tx+D rats (from 55.6±1.9 g to 56.1±2.7 g). As expected, glycemia was higher in the D populations, both intact and Tx *vs.* their respective C rats (Table II). After Tx, glycemia increased in C rats, not in D rats. All the D rats showed a decrease in plasma insulin as compared to their respective C or C+Tx rats (Table II).

After Tx, plasma and hypothalamic T4 and T3 concentrations were decreased in C and D rats and diabetes diminished plasma T4 and T3, specially at 45 days (Table II). Hypothalamic T3 content was also decreased in D and D+Tx rats, at both ages studied, as compared to their respective C and C+Tx rats while hypothalamic T4 decreased only at 45 days (Table II). The determination of T3 and T4 in pituitary of both Tx populations fell below the RIA detection threshold.

Calculated plasma T3/T4 ratio was not changed by diabetes or thyroidectomy and was only significatively higher at 35 than at 45 days of life for the C+Tx rats (0.06±0.006 *vs* 0.027±0.006). The hypothalamic T3 / T4 ratios were always higher than the plasma T3 / T4 ratios (more than 10-fold) and were also higher at 35 than at 45 days of life in C and C+Tx animals, while D and D+Tx rats maintained the same ratios at both ages. The hypothalamic T3 / T4 ratio decreased by 70% in Tx+D rats *vs* D rats (0.38 *vs* 1.14) at 10 days after Tx, as opposite to the values

Table I: *Glycemia, insulinemia and hypothalamic and pituitary 5'-deiodinase II (5'D-II) activity in diabetic and control neonatal rats.*

Values are means ± S.E. [a]p<0.05 relative to control rats of the same age. [b]p<0.05 relative to consecutive older rats for corresponding control or diabetic group. In parenthesis, number of animals studied.

| Age (days) | 8 | | 14 | | 23 | |
|---|---|---|---|---|---|---|
| Glycemia (mg/100ml) | | | | | | |
| Control | 105.6 ± 2.1 | (7) | 110.8 ± 2.3 | (9) | 121.3 ± 3.4 | 9) |
| Diabetic | 272.5 ± 11.5[a,b] | (10) | 205.0 ± 18.3[a,b] | (9) | 293.4 ± 14.1[a] | (9) |
| Insulinemia (μU/ml) | | | | | | |
| Control | 42 ± 5.2 | (7) | 48.2 ± 6.0 | (8) | 48.4 ± 6.0 | (8) |
| Diabetic | 33 ± 10.5 | (9) | 31.7 ± 3.3[a] | (16) | 32.7 ± 7.5[a] | (16) |
| Pituitary 5'D-II (fmol /h/mg prot) | | | | | | |
| Control | 122.2 ± 8.5 | (9) | 123.9 ± 11.3[b] | (8) | 224.7 ± 14.5 | (7) |
| Diabetic | 68.4 ± 4.5[a] | (10) | 88.5 ± 13.4 | (11) | 100.6 ± 5.8[a] | (16) |
| Hypothalamus 5'D-II (fmol/h/mg prot) | | | | | | |
| Control | 16.4 ± 0.9 | (16) | 16.5 ± 0.6 | (12) | 14.4 ± 0.8 | (7) |
| Diabetic | 2.7 ± 0.5[a,b] | (10) | 11.2 ± 1.2[a] | (10) | 12.1 ± 0.5 | (9) |

observed in the C+Tx groups (1.64 *vs* 1.29 in C).

The hypothalamic to plasma ratios were also calculated, using pools of hypothalamus and plasma from the same animals. Diabetes increased the hypothalamic to plasma T4 ratio by 2-fold at 35 days (0.21±0.02 *vs* 0.1±0.01 in C rats) and by 7-fold at 45 days (1.25±0.27 *vs* 0.17±0.04 in C rats), and this ratio increased 6-fold with the length of diabetes. This suggests that diabetes increases the uptake of T4 into the hypothalamus in a time-dependent manner. Hypothalamic to plasma T3 ratios were increased 6-fold in C+Tx rats at 35 days and in the D group 3-fold at 45 days, but these increases were absent in the D+Tx group.

Thyroidectomy induced the expected increase in plasma TSH at 10 and 20 days after,which that was smaller in D than in C animals, although the basal plasma TSH values were the same in both populations at both ages (Table III). Pituitary TSH content in D and D+Tx rats, was always lower than in C and C+Tx rats, being higher in D+Tx animals (at both ages) than in D rats. This increase was not found in C+Tx rats (Table III). Pituitary TSH did not increase between 10 and 20 days after Tx in D rats.

At 35 days of age, pituitary 5'D-II activity was higher in D than in C rats (Table III), and, as expected, increased in response to Tx in C and D. This increase was lower in D than in C rats at 35 days and higher than in C rats at 45 days. Consequently, at 35 days the increase above the basal 5'D-II activity was smaller in D+Tx (2.3-fold) than in C+Tx rats (4.4-fold), but at 45 days the increase was higher in D+Tx (5.35-fold) than in C+Tx rats (4.4-fold).

As found in the pituitary, hypothalamic 5'D-II activity was higher in D than in C rats at 35 days of age (Table III),

Table II: *Effect of thyroidectomy (Tx) on glycemia, insulinemia, T4 and T3 concentrations in plasma and hypothalamus in diabetic and control adult rats.*
Values are means ± S.E. [a]$p < 0.05$ relative to C rats on the same day. [b]$p < 0.05$ relative to older rats for respective C or D group. [c] $p < 0.05$ relative to Tx rats for the same group. In parenthesis, number of animals. Hypothalamus were pooled.

| Days after Tx | 10 | | 20 | |
|---|---|---|---|---|
| Glycemia (mg/100ml) | | | | |
| Control | 101.2 ± 5.7[c] | (10) | 105.0 ± 4.8[c] | (10) |
| Control + Tx | 116.0 ± 3.7 | (12) | 129.6 ± 6.55 | (10) |
| Diabetic | 403.1 ± 9.5[a,b] | (10) | 358.6 ± 16.4[a] | (8) |
| Diabetic + Tx | 394.6 ± 10.5[a] | (9) | 395.2 ± 13.6[a] | (9) |
| Insulinemia (μU/ml) | | | | |
| Control | 48.6 ± 3[c] | (12) | 50.6 ± 2.2 | (12) |
| Control + Tx | 40.3 ± 2[b] | (10) | 50.4 ± 2.3 | (10) |
| Diabetic | 34.6 ± 6.1[a] | (8) | 35.6 ± 9.0[a] | (9) |
| Diabetic + Tx | 33.9 ± 4.9[a] | (10) | 35.6 ± 8.0[a] | (10) |
| Plasma T4 (ng/ml) | | | | |
| Control | 21.853 ± 4.030[c] | (5) | 15.982 ± 2.446[c] | (5) |
| Control + Tx | 3.01 ± 0.200[b] | (5) | 5.175 ± 0.615 | (5) |
| Diabetic | 10.18 ± 0.18[a,b,c] | (5) | 1.307 ± 0.244[a,c] | (5) |
| Diabetic + Tx | 4.860 ± 1.370[a,b] | (5) | 0.784 ± 0.063[a] | (5) |
| Plasma T3 (ng/ml) | | | | |
| Control | 0.916 ± 0.040[b,c] | (5) | 0.488 ± 0.077[c] | (5) |
| Control + Tx | 0.150 ± 0.062 | (5) | 0.126 ± 0.012 | (5) |
| Diabetic | 0.404 ± 0.026[a,b,c] | (5) | 0.190 ± 0.058[a,c] | (5) |
| Diabetic + Tx | 0.241 ± 0.041[b] | (5) | 0.043 ± 0.004 | (5) |
| Hypothalamus T4 (ng/g) | | | | |
| Control | 2.090 ± 0.079[b,c] | (5) | 2.757 ± 0.082[c] | (5) |
| Control + Tx | 0.539 ± 0.023 | (5) | 0.612 ± 0.114 | (5) |
| Diabetic | 1.911 ± 0.132[c] | (5) | 2.199 ± 0.294[a,c] | (5) |
| Diabetic + Tx | 0.514 ± 0.031 | (5) | 0.498 ± 0.052 | (5) |
| Hypothalamus T3 (ng/g) | | | | |
| Control | 2.700 ± 0.122c | (5) | 2.475 ± 0.035[c] | (5) |
| Control + Tx | 1.103 ± 0.246 | (5) | 0.863 ± 0.215 | (5) |
| Diabetic | 1.990 ± 0.028[a,b,c] | (5) | 1.841 ± 0.083[a,c] | (5) |
| Diabetic + Tx | 0.195 ± 0.029[a] | (5) | 0.236 ± 0.049[a] | (5) |

Table III: *Plasma and pituitary TSH, and 5'D-II activity in pituitary and hypothalamus of diabetic (D) and control (C) adult rats.*
Values and symbols as in Table II.

| Days after Tx | 10 | | 20 | |
|---|---|---|---|---|
| Plasma TSH (ng/ml) | | | | |
| Control | 0.9 ± 0.09[b,c] | (7) | 1.2 ± 0.1[c] | (7) |
| Control + Tx | 25.9 ± 2.0[b] | (7) | 35.2 ± 0.9 | (5) |
| Diabetic | 0.7 ± 0.08[b,c] | (5) | 1.1 ± 0.02[c] | (5) |
| Diabetic + Tx | 16.0 ± 1.3[a] | (5) | 17.3 ± 2.4[a] | (5) |
| Pituitary TSH (µg/gland) | | | | |
| Control | 1.6 ± 0.2 | (5) | 1.4 ± 0.2 | (8) |
| Control + Tx | 1.3 ± 0.1[b] | (6) | 1.7 ± 0.1 | (7) |
| Diabetic | 0.5 ± 0.07[a,c] | (6) | 0.6 ± 0.1[a,c] | (5) |
| Diabetic + Tx | 0.9 ± 0.09[a] | (7) | 1.0 ± 0.1[a] | (6) |
| Pituitary 5'D-II (fmol/h/ mg prot) | | | | |
| Control | 246 ± 11[c] | (9) | 211 ± 14[c] | (10) |
| Control + Tx | 1073 ± 123 | (10) | 935 ± 80 | (10) |
| Diabetic | 336 ± 25[a,b,c] | (6) | 234 ± 10[c] | (6) |
| Diabetic + Tx | 759 ± 102[b] | (6) | 1253 ± 178[a] | (5) |
| Hypothalamic 5'D-II (fmol/h/mg prot) | | | | |
| Control | 9.2 ± 0.8 [c] | (6) | 14.8 ± 3.2[c] | (12) |
| Control + Tx | 146 ± 7[b] | (7) | 88.8 ± 4.5 | (10) |
| Diabetic | 33 ± 2[a,b,c] | (7) | 12.6 ± 2.4[c] | (6) |
| Diabetic + Tx | 139 ± 10[b] | (6) | 81.0 ± 3.2 | (6) |

but this increase was not found at 45 days of life. Hypothalamic 5'D-II activity increased in response to Tx at a same rate in C and D rats. Hypothalamic 5'D-II activity decreased between 35 and 45 days of life in Tx animals, both D or C (Table III). The increase above the basal hypothalamic 5'D-II activity was lower in D+Tx (4.2-fold) than in C+Tx rats (15.9-fold) at 35 days, and this difference disappeared at 45 days (6.4-fold in D+Tx and 6.0-fold in C+Tx rats).

## Discussion

In the present paper we studied whether diabetes induced during early development, affects 5' deiodinase activity in pituitary and hypothalamus. It is shown for the first time that 5'D-II activity is decreased in pituitary and hypothalamus of neonatal D rats, and that the ontogenic patterns for 5'D-II in both tissues are delayed in D rats during an important period for brain development.

During this period brain T4 and T3 concentrations reach maximal values (23, 33) and many important maturation processes occur in the brain. The decrease found in pituitary and hypothalamic 5'D-II activity from neonatal D rats is more pronounced than previously found in neonatal undernourished rats (26), in which variations in pituitary and hypothalamic 5'D-II activity are minimal. In the present study hypothalamic 5'D-II in D rats tends to increase and becomes normal by the 3rd week of life, but we do not know if this is due to a delayed developmental increase in 5'D-II or to some regeneration of the pancreatic β-cells (6), that has been described in induced diabetes around birth (19), due to the capacity of b cells to proliferate at these early stages. However, in our study no amelioration of diabetes is observed as measured by insulinemia or glycemia. The decrease we find in pituitary and hypothalamic 5'D-II should be considered when studying the consequences of non-thyroidal syndromes on the thyroid axis during development.

Due to the difficulties found in the survival of neonatal D rats and the small size of the samples, we studied the effect of diabetes and the response to Tx in young rats in which diabetes was induced at 23 days of life.

In the 2nd experiment diabetes was confirmed by elevated glycemia, decreased insulinemia and lower BW. Plasma and hypothalamic T3 and T4 were also decreased, except for hypothalamic T4 at 35 days of life which was maintained at the expenses of an increased uptake of T4, as 5D-III is not decreased in the brain of pregnant D rats (5). At 35 days of age, hypothalamic, as well as pituitary, 5'D-II activity was elevated in D versus C rats, possibly as an early reaction of the hypothalamus to the diabetic state. These increases could be responsible for the normal T3 to T4 ratio in hypothalamus of D rats at 35 days of life, but even so, were not able to maintain normal T3 concentrations in hypothalamus, that were decreased by 30%. So, 5'D-II in hypothalamus and pituitary is not insensitive to diabetes, as previously reported for brain or pituitary (11, 25, 34), but seems to respond with decreases in the neonatal period or even increases (as in hypothyroidism) during early phases of diabetes in young rats.

Diabetes induces some incapacity on the hypothalamic and pituitary 5'D-II activity to respond to Tx. All the found changes, not reflected in the plasma T3/T4 ratios, underscores the importance of the determination of T3 and T4 concentrations in hypothalamus as compared with conclusions drawn from circulating thyroid hormone levels. The decrease found in plasma and hypothalamic T4 and T3 are more pronounced than those found in undernourished neonatal rats (26).

A relevant fact to consider in the thyroid axis regulation in undernutrition and diabetes, is the presence of low circulating TSH levels along with reduced thyroid hormones (1, 13, 26, 30, 34) contrary to what occurs in hypothyroidism. Pituitary TSH levels depends mainly on a balance between the stimulatory action of TRH on TSH synthesis and secretion and the inhibitory role of T3 on TSH secretion and TRH synthesis (4, 10). Tx induces a marked increase in prepro-TRH concentrations in the paraventricular nuclei and median eminence areas which are involved in TSH regulation (41) and experimental hypothyroidism causes a significant increase in hypothalamic TRH release in rats (31). On the other hand, T3 is able to control TRH synthesis through its inhibition of the negative thyroid responsive elements (TREs) in the TRH promoter (15).

In D animals, the hypothalamic TRH content (13) and release (7, 30) have been described to be decreased, a fact that seems to contribute to the decreased pituitary TSH content. The fact that the pituitary TSH content increases in D+Tx, indicate that this is due to an increased release of TRH, together with the lower hypothalamic T3 levels. In fact, the plasma TSH released in response to Tx was lower in D+Tx rats than in C+Tx. This response could be attributed to a lower TRH release in D rats (30), together with an increased sensitivity of the pituitary to T4 in diabetes (13), as lower T4 doses are required to suppress TSH secretion. This data highlights the role of pituitary and hypothalamic T3 content and of 5'D-II activity in the regulation of pituitary TSH content in the euthyroid sick syndromes.

The fact that pituitary TSH content increases after Tx in D, as well as in undernourished rats (13) supports the idea that the lower increase of 5'D-II activity in D rats could be a decisive factor in the regulation of pituitary TSH content by TRH. Thus, changes in pituitary and hypothalamic 5'D-II activity could play a role in the accumulation of pituitary TSH in thyroidectomized D and undernourished rats. The complex metabolic and endocrine changes induced by diabetes complicates the study of thyroid axis regulation, but the results reported here in D populations after Tx, together with those of undernourished rats, already published (26), point to the important role of subtle physiological signals which regulate TSH gene expression in pituitary.

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En ratas diabéticas (D) por tratamiento con estreptozotocina (STZ) se investiga la influencia de la actividad hipotalámica e hipofisaria 5'-desiodasa tipo II (5'D-II) y el nivel de T3 sobre el contenido hipofisario de TSH. Los resultados muestran que la actividad 5'D-II en hipotálamo e hipófisis es menor en ratas D neonatales que en las controles (C) y que el patrón de desarrollo de la actividad 5'D-II está alterado. Además, cuando ratas D y C son tiroidectomizadas (Tx) a los 25 días de vida (D+Tx, C+Tx), la actividad 5'D-II hipotalámica e hipofisaria aumenta en ambas poblaciones Tx frente a ratas intactas, pero el aumento es menor en las D+Tx que en las C+Tx. La relación T3/T4 en hipotálamo es tambien menor en ratas D+Tx (0,38) que en las C+Tx (1,64). El contenido hipotalámico de T3 disminuye en un 30% en D respecto a C y en un 80% en D+Tx respecto a C+Tx, mostrando un defecto en la desiodación hipotalámica de T4. El contenido hipofisario de TSH aumenta tras tiroidectomía sólo en las ratas diabéticas (D+Tx), pero no en C+Tx. Estos resultados indican que la actividad hipotalámica e hipofisaria de 5'D-II y el contenido hipotalámico de T3 se afectan por la diabetes e intervienen en la regulación del contenido hipofisario de TSH.

**Palabras clave:** Diabetes, Desiodación, TSH.

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